INNOVATION • ADVANCEMENT • DISCOVERY • 85 Years VA Research 1923 - 2008

VA RESEARCH: IMPROVING VETERANS' LIVES

A Historical Look

at the Establishment of the

Department of Veterans Affairs Research & Development Program

www.research.va.gov

Veterans Health Administration
Research & Development
Improving Veterans' Lives -- www.research.va.gov

A Historical Look at the Department of Veterans Affairs Research and Development Program

Acknowledgement to Author

This book was compiled and written by Marguerite T. Hays, M.D., for the VA Office of Research & Development (ORD). ORD is grateful to the author, Dr. Hays, for her relentless work and dedication to make this publication possible. Her outstanding efforts as a physician, researcher, and writer have produced a lifetime of invaluable information about the inception of VA research. We are proud to present this book to the VA and non-VA community alike.

Table of Contents

Preface

In 1988, I was having lunch with Ralph Peterson, M.D., a prominent endocrinologist who was then the Director of the VA's Medical Research Service, a position I had held during the 1970s. As I told him about events from before he joined the VA, he was struck how little information had been written about earlier times in the VA research program. A few days later, he called to ask me to give a talk on the history of the VA research program.

Challenged by this opportunity, I began to interview some of the earlier participants in the program and found their stories fascinating. I explored the VA Central Office library in Washington, DC and discovered another side to the dark memories of the early Veterans' Bureau, evidence that the early veterans' doctors strived for excellence and looked for ways to improve their care of sick veterans.

As opportunities arose, I interviewed people associated with the VA research program. I collected the materials they gave me, some of it lovingly stored in their garages for years. Many in the VA, in Central Office and in the medical centers, participated in this effort – there is no way I can thank them individually here, but I am grateful to each of them.

This work continued to be encouraged and supported by those who came after Ralph Peterson in leading the VA research program. In particular, I should mention Martin Albert, M.D., Ph.D., who, as Director, Medical Research Service, 1992-1996, was especially helpful. John Feussner, M.D., Chief Research and Development Officer, 1996-2002, supported this effort with his usual enthusiasm. He contracted with me to bring the work to fruition after I retired from my VA clinical position. Philip Lavori, Ph.D., Chief of the Palo Alto VA Cooperative Studies Program Coordinating Center, provided space and facilities for the project and has been of great personal support.

Anne Knight, Barbara Klein and Robert Putnam, editors, have improved the quality of the text in many ways, and Dorothy Shoemaker has provided important bibliographic assistance. Many colleagues were kind enough to review individual chapters. Joel Braslow, M.D., Ph.D., made important contributions to the chapter describing VA psychopharmacology trials. I owe particular thanks to the late Clark Sawin, M.D., for a careful and helpful review of the entire manuscript. Of course, the responsibility for the final product rests with me.

Marguerite T. Hays, M.D.
Palo Alto, CA

Introduction

Tracing the path of progress in VA medical research does not involve drawing a straight line. It requires, rather, sketching a jagged streak forward—the many high points marked by significant findings and the development of medical advances, the few downticks indicating an occasional disappointment—the trend always upward toward promise and hope for improved health care and a better quality of life.

The focus of this history is the innovation produced in this remarkable program; a few examples of what VA research has accomplished include the:

- First decisive trials of effective treatments for tuberculosis;
- Demonstration of the lifesaving value of treating hypertension;
- Development of the concept of CT scanning;
- Discovery and development of radioimmunoassay, facilitating measurements of previously impossible precision;
- Cooperative studies proving the efficacy of psychoactive drugs in stabilizing psychiatric disorders;
- Demonstration of the relationship between smoking and lung cancer, leading to initial warnings in the Report of the Surgeon General; and
- Development of a practical, implantable cardiac pacemaker.

Although this research program produced more than enough accomplishments to completely occupy its text, this history also attempts to depict the pioneers who carved that path of progress. In large measure, the history of VA medical research is their story.

In several instances, personal comments are included from the men and women—investigators, managers and administrators—who brought VA research alive. Some of their accounts are truly fascinating, sounding more like adventure stories than what might appear in scientific journals. For example, Ludwig Gross, M.D., a war refugee who escaped Poland just ahead of the Nazis, came to America and became a U.S. Army doctor. Even while in the Army, he carried out research, keeping his special mice in cages in the trunk of his car. In 1944, the Army assigned him to the clinical staff of the Bronx (NY) VA Hospital, and he remained there for a long productive career. At first, he did his research in an old bathroom after hours, breeding his own mice for his experiments. His work led to the proof of the viral cause of mammalian leukemia.

And, when Dr. William Oldendorf was working as a VA neurologist at the Los Angeles VA Hospital, he was looking for a way to avoid suffering by his patients who needed brain imaging, rather than doing painful pneumoencephalography. He reasoned that composite pictures of the brain area from x-ray images taken at many angles would serve the purpose. Using simple equipment—including an old model-railroad track—he personally built the prototype for CT scanning—which has since benefited millions of patients worldwide.

Some few of these researchers achieved a degree of celebrity, gaining eminence in their field, and perhaps even becoming perceived in the general medical community as having extraordinary genius

and exceptional vision. There are many more stories of researchers whose careers reflect little of celebrity, but much of imagination, competence, and intense excitement about their work.

The personal stories reveal another important characteristic of these investigators: the patience with which they approached the mundane tasks along the way to achieving results. Records clearly indicate that "payoffs" in scientific knowledge often emerged only after extensive, long-term follow-through study. The keys to success were determination to proceed, to persist, to prevail. As one VA research leader said, "there were more 'wear-throughs' than breakthroughs."

A word about the scope of this book is in order: the recording of history is a never-ending process, but preparation for publication must have an organized, terminal point. In covering the more distant history of VA medical research—extending back to the era of the Veterans' Bureau in the late 1920s—through the year 1980, it was the intention of this work to record and, in some sense, safeguard that period of history most at risk of being lost to posterity.

Unlike this text, VA research did not conclude in 1980. Together with Health Services Research and Development, and Rehabilitation Research and Development, the VA Medical Research Service continues to evolve and to engage in vitally important studies. Investigation of primary clinical issues continued, and new special studies were launched in areas of special interest to the veteran patient, such as post-traumatic stress disorder, "Gulf War Syndrome," prostate cancer and AIDS. Between records developed since 1980, the personal knowledge of the current VA staff, and the recollections of those who have departed in recent years, the story of this continued history exists in rich detail. It can only be hoped that this next chapter of the story of VA research will be recorded and told.

That, however, is a matter for future exploration. For now, the story of the beginnings of VA medical research, and its truly remarkable accomplishments over the span of its first half-century, should be adventure enough.

Commonly used acronyms

The organization responsible for veterans' health care

VA (1930-1989)	Veterans Administration
VA (1989 to present)	Department of Veterans Affairs
VACO	VA Central Office

The Office in VACO specifically responsible for the veterans' medical care program

DM&S (1946-1989)	Department of Medicine and Surgery
VHA (1989 to present)	Veterans' Health Administration

Head of the VACO office responsible for veterans' medical care

CMD (1946-1989)	Chief Medical Director
USH (1989 to present)	Under Secretary for Health

Head of the VACO office overseeing the VA research program

ACMD/R&E (1945 to 1972)	Assistant Chief Medical Director for Research and Education
ACMD/R&D (1972 to 1989)	Assistant Chief Medical Director for Research and Development
AsCMD/R&D (1989 to 1996)	Associate Chief Medical Director for Research and Development
CRADO (1996 to present)	Chief Research and Development Officer

Person at a VA medical facility responsible for the research program

ADPSR (1947 to1961)	Assistant Director of Professional Services for Research
ACOS/R&E (1961 to1972)	Associate Chief of Staff for Research and Education
ACOS/R&D (1972 to present)	Associate Chief of Staff for Research and Development

Services within Research and Development in VACO (after 1972)

MRS	Medical Research Service
HSR&D	Health Services Research and Development Service
RER&D, later RR&D	Rehabilitation (Engineering) Res. and Dev. Service

Advisory and review groups

Local:

R&E Committee (1948 to 1972)	Research and Education Committee
R&D Committee (1972 to present)	Research and Development Committee

Central

CVMP	Committee on Veterans' Medical Problems (NAS/NRC)
RAC	Research Advisory Committee
RRAG, later RAG	(Regional) Research Advisory Group
CSEC	Cooperative Studies Evaluation Committee
MRB	Merit Review Board

Other VA acronyms

R&D	Research and Development
CRIP	Central Research Instrumentation Pool
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CNPRL	Central Neuropsychiatry Research Laboratory

Other Washington area groups influencing the VA research program

CMR	Committee on Medical Research (WWII)
NAS	National Academy of Sciences
NRC	National Research Council of the NAS
OMB	Office of Management and Budget
NIH	National Institutes of Health
NCI	National Cancer Institute

Not abbreviated: Veterans' Bureau (1922-1930), Medical Service (1922-1946), Medical Director (1922-1946), Chief, Research Subdivision (1925-1938), Chief, Postdoctoral Training and Research Division (1938-1945).

Section I. Ancestral Roots
1925-1945

(Intentionally Blank)

Chapter 1. Origins of the VA Research Program, 1917-1925

America's tradition of providing medical care to the nation's servicemembers and Veterans is a well-documented subject, with origins reaching back to Colonial times. The federal government has frequently modified and clarified its role in this area during the course of over two centuries of our democracy, acting through legislation and executive orders to form the institutions and programs that identified the recipients and established the mechanisms to provide medical service. History also records the way in which distinctions have been established between systems of care for active-duty personnel and those whose service is completed—our Veterans.

While the evolution of federal programs for the delivery of post-service care to Veterans is well charted, the point at which medical research became an important consideration is less defined. No direct act of the legislative or executive branches of government dictated that Veterans' health care could be enhanced with a research component. The association of research and clinical care grew mainly from the wisdom and foresight of medical practitioners themselves. Records from the earliest meetings of advisors and consultants charged with addressing large-scale medical needs among Veterans after World War I reveal gathering convictions that research could and should be integrated into Veterans' health care. Beyond the positive benefit of relating that research to the unique medical circumstances of Veterans, the move was seen as key to reinforcing an evolving system of care. Many of these advisors felt that making the system attractive to physicians with research interests and cultivating relationships with medical education institutions would ensure the highest quality of care to Veterans.

In the era well before 1946 when the Veterans Administration (VA) established formal partnerships with medical schools, the Veterans' Bureau and its successor, the Veterans Administration, sponsored a modest program of intramural research by their own clinical staff. This early VA research program almost completely disappeared during the Second World War. After World War II, a rejuvenated VA medical care system emerged as a result of post-war reforms that included affiliation of VA hospitals with medical schools. Relatively few links between the research program of the 1920s and 1930s and the later emergence of medical research in the VA after World War II survived the enormous societal upheavals that affected not only VA but medicine in general. Nonetheless, these early efforts did provide a valuable and noteworthy prologue for what would come later.

The foremost goal of early Veterans' Bureau advisors forming an intramural agency research program was to "mine" rich clinical data to gain knowledge through follow-up studies and population statistics of a large system with many patients of similar backgrounds. The administrators were especially interested in problems caused directly by wartime service, such as long-term effects of poison gases encountered on the battlefield. And clinicians in the Veterans' hospitals were deeply concerned about helping these patients by studying their most prevalent medical problems regardless of whether they were the direct result of military service.

The early research program of the veterans' hospital system emerged from the combined influence of a reform-minded lay bureau Director, a Chief Medical Officer considered to be ambitious and politically knowledgeable, an influential group of advisors with strong bonds to academia, and a cadre of medical officers in the veterans' hospitals who used the means at their disposal to seek

better ways to treat their patients. These people are at the heart of events that identified the need for reform, and the academically-oriented advisors they consulted shaped that reform.

Beginnings of systematic health care for disabled Veterans

In 1917, upon America's entry into World War I, more than 5 million men were in military service, but no hospitals existed specifically for Veterans. .[1] By the end of 1925, amazingly, 51 hospitals for Veterans had been established and some 30,000 Veterans were hospitalized at government expense.[2] Before World War I, Congress did not appear inclined to create a hospital system specifically for veterans, much less to launch a program of medical research for their special needs. Indeed, although some Veterans had been treated under government auspices in the past, the very concept that the federal government should handle the medical needs of *all* war-disabled Veterans was a new one in 1917.[3]

In 1923, a committee of consultants appointed by the Secretary of the Treasury described the 1917 provision for hospitalization of World War Veterans as "a task which had never been attempted by any government prior to that time, and there had been no experience in all history which could serve as a guide."[4] While the United States had long provided pensions for its disabled war Veterans, until after World War I there were no systematic arrangements for their later medical care. Sick merchant seamen had been cared for in Marine Hospitals since 1799.[5] A few thousand indigent Civil War and Spanish-American War Veterans lived in national or state-supported domiciliaries or Soldiers' Homes.[3] Otherwise, before 1917, disabled Veterans did not receive medical care from their government. Those injured or ill from military service received monetary compensation in the form of pensions. Their families, aided by the medical and hospital systems available to all citizens, were expected to meet their needs for medical care and rehabilitation.

The pension system for Civil War Veterans had been very costly and was subject to intense and continuing political pressures.[6] In 1917, Secretary of the Treasury William McAdoo, President Wilson's son-in-law,[7] appointed a Council on National Defense, which had a subcommittee charged with drafting a plan to meet the needs of the men about to go to war. Judge Julian W. Mack, a distinguished jurist and advocate for the disadvantaged, chaired this subcommittee. Other members included Dr. Leo S. Rowe, Assistant Secretary of the Treasury; Captain H.S. Wolfe, a prominent accountant and actuary; Julia C. Lathrop, of the Children's Bureau; V. Everit Macy, President of the National Civic Federation; Professors Henry R. Seager and Thomas Parkinson of Columbia University; and the staff of the Legislative Drafting Research Fund of Columbia University.

Under Judge Mack's leadership, this group recommended a radically new concept of government responsibility and sent a draft for review to interested persons, including President Wilson and former President Theodore Roosevelt, who both enthusiastically endorsed it.[8] The concept entailed government aid to former soldiers and sailors based on their needs and the impact of military service on their lives; unlike the Civil War pensions, this aid was not seen as a dole provided simply because of military service. This plan was introduced as a Treasury Department bill and passed into law October 6, 1917. While completely omitting pensions for World War Veterans and their families, the new law provided for:

- Allotments to dependents while their breadwinner was on military duty, paid partly from pay deductions.
- A voluntary death and disability insurance program, with premiums set at peacetime rates, funded by pay deductions. (This deduction and the previously mentioned one often took up most of the soldier's pay, and could leave the veteran less than $10 a month.[9])
- Compensation for injuries sustained while on active service and compensation to the families of those who died.
- Vocational rehabilitation for those injured.

Perhaps most importantly, for the first time, the law provided for the medical and surgical treatment and prosthetic devices for all service men and women who were injured or became ill in the line of duty. [8, 10]

This massive new program became the responsibility of the Bureau of War Risk Insurance, an agency separate from the old Pension Bureau, which continued to handle pension claims of Veterans of earlier wars and their dependents. In October 1917, the Bureau of War Risk Insurance, which had been established in 1914 to insure merchant ships against wartime aggression, was a modest operation with only 20 employees occupying four rooms.[8] Despite wartime shortages of personnel and space, the Bureau expanded rapidly to meet its new challenges. Until the armistice of November 11, 1918, most of the Bureau's new work involved selling insurance policies to servicemen, processing insurance claims and paying allotments to families and compensation payments for injury and death. Until the end of the war, medical care and rehabilitation were handled by military hospitals,[11, 12] but discharged Veterans still needing care were dependent on the Bureau.

It seems unlikely that the members of Congress who voted for this sweeping restructuring of Veterans' benefits fully realized that a separate veterans' hospital system was being created. In fact, Congress did not appropriate any money to build new hospitals for Veterans until 1921. Nevertheless, this bill was the seed for today's comprehensive system of Veterans' health care.

World War I was the first U.S. war in the modern era of hospital care. In the 19th century, hospitals were considered charitable institutions for the impoverished. Other sick and injured persons were treated in their own homes. Military hospitals during the Civil War treated huge numbers of the sick and injured, but after discharge Veterans did not expect or receive hospitalization. Early in the 20th century, with the introduction of improved surgical techniques, increased medical specialization, and the use of clinical laboratories and radiology, hospitals became places for all the sick, the rich as well as the poor.[13] So it was that a nation that in the past expected families and communities to care for the war-disabled, as long as pensions spared them from penury, suddenly expected Veterans' care to be provided in government hospitals.

At the end of the war, many patients being treated in military hospitals demanded to be released from active duty. Of those discharged, about 2,500 had tuberculosis and 50,000 were classified with nervous and mental disorders.[14] Suddenly, the many sick and injured became the medical responsibility of, and expected medical care from, the Bureau of War Risk Insurance, which was not prepared to handle them. Since the Bureau had no hospitals or doctors of its own, it turned to the Public Health Service for use of its Marine Hospitals. In 1919, the Marine Hospital system had a capacity of only 1,548 beds but was expected to handle 20,000 applications for hospitalization.[14]

A disabled Veteran applying to the Bureau of War Risk Insurance for medical care would first be subject to a determination of eligibility that would place him in the hands of the Public Health Service. If there was room at a Marine Hospital, care would be provided there. But in the early stages of this program, many Marine Hospitals were full, so the patient might end up at a Soldiers' Home infirmary or in a private or state hospital. Often these were also full, and some were not considered suitable to provide an acceptable level of care for deserving Veterans.

In 1919, Congress tried to correct the shortage of Veterans' hospital beds by authorizing transfer of a group of military hospitals to the Public Health Service and the purchase or construction of additional military hospitals. But transferred hospitals were mostly of temporary construction, and many were unusable. Still, some members of Congress believed that the huge Army hospitals built during the war, even though intended to be temporary, should be used to serve Veterans' needs and did not appropriate the funds needed to carry out the authorized construction.[15] By 1921, no new veterans' hospitals had yet been constructed.[16] Even with the hospitals that had been transferred to the Public Health Service, there wasn't enough room for the disabled Veterans. Public attention to the problem was growing as newspapers carried pictures of sick Veterans lying on the floors of jails and almshouses.[17]

Finally, in 1921, Congress acted. On March 4, 1921, on his last day in office, President Wilson signed Public Law 384, later referred to as the first Langley bill. It provided $18.6 million for constructing new veterans' hospitals and remodeling and extending existing plants.[16] This construction program was one of the first responsibilities of President Harding's new Secretary of the Treasury, A.W. Mellon, whose department included both the Public Health Service and the Bureau of War Risk Insurance. To assist in this task, Mellon appointed a Committee of Consultants, generally known as the White Committee after its chairman, William C. White, M.D. (Appendix IIa).

The Consultants, together with their advisory committee, traveled widely, visiting the institutions caring for ex-servicemen. They gathered an extensive body of data, including the distributions of general and Veteran population, existing government and nongovernment hospitals, access to transportation and predictions of future needs. They also corresponded extensively with and held hearings of, "interested groups." As noted in their report:

> "In addition to the task of assembling available data, there were requests for hearings from over 100 groups—Senators, Representatives, State and municipal committees, chambers of commerce, etc.—representing those interested in the location of hospitals in their particular districts. These scarcely provided the data on which to build a rational Federal program, but all were heard."[18]

Members of the White Committee were from academic settings, suggesting that the Committee would favor placing new veterans' hospitals near medical schools. But this did not happen, and the final report sheds light on how committee members came to a critical turning point in their work:

> "What would secure for the beneficiaries of the Government the best type of medical service? Should they be confined solely to isolated Government institutions, or should they have available such consultant and expert advice as surrounds the best type of teaching institutions? Which would secure the most rapid recovery and return to active participation in the duty of life? Here again, the tendency was all for centralization in Government institutions, in spite of the fact that there had been gathered from all over the United States the willingness and desire on the part of those institutions which had devoted themselves to the care of the public to assist in this work. This tendency to centralize had grown so rapidly and the change in administration had come about so quickly that it was impossible to wield any influence in securing special care by physicians who had become highly expert in special technique for the benefit of these men, and, although in the location of these hospitals the consultants had constantly in mind that they should be as near as possible to centers of medical education and assistance of this character, it was felt that the effort was largely wasted.
>
> "There was an opinion frequently expressed that our soldiers were not to be submitted to experiment and student teaching, and yet the very best type of medical care given is in those institutions that come under the critical eye of students and in which teaching is carried on—to wit, Johns Hopkins, Harvard, Columbia, Chicago, and elsewhere—and it is a duty of our Government, where possible, to accept its share in opening the doors of these institutions for instruction of oncoming doctors and nurses who will in the future have to deal with those who are sick.
>
> "In an attempt to solve these questions the consultants found great difficulty, because of the variation of expert opinion. Men of equal prominence and success in life at times presented diametrically opposite views, and the only conclusion that could be drawn was that in fields involving human activity, where positive knowledge was not available, no standards could be set, and any attempt to standardize human organization could only be met with failure. Each institution in its administration is a separate institution, modified by the locality in which it exists, the views of the Chief Officer of Administration, and the task which it has to perform, and it is impossible to lay down standards that will universally apply. To overcome this difficulty a request was made that the medical director for each institution be chosen during the process of construction, so that the Supervising Architect's Office should have his advice continuously in securing an institution which would fill his administrative point of view."[19]

While in some cases Committee members undoubtedly succumbed to pressures for their decisions, the White Committee also actively sought out suitable locations for Veterans' hospitals. In May 1921, the month after the Committee originally received its charge, member Frank Billings sent the following telegram to Ray Lyman Wilbur, M.D., who was then president of Stanford University:

> "Will local people buy and present to government 100 or more acres to afford additional ground space to existing federal owned property to insure location of permanent government hospital at Palo Alto? Letter follows. Wire or write reply to Dr. W.C. White, C/O Bureau of War Risk Insurance, Arlington Building, Washington."[20]

One week later, Dr. Wilbur answered:

> "Very appreciative of telegram and letter of Dr. Billings regarding Federal Hospital Palo Alto. Have consulted with Palo Alto Chamber of Commerce and feel that if your committee decides upon this as a permanent site Palo Alto Chamber of Commerce will raise sufficient subscription to pay differences so that fifty to one hundred acres adjoining present site can be purchased at cost to Government of $600 per acre. Community small but fully sympathetic with hospital and will do their best. Would appreciate opportunity to do anything further if I can."[21]

In due time, one of the White Committee's new hospitals was placed in Palo Alto, a hospital that continued to be of great interest to Dr. Wilbur.

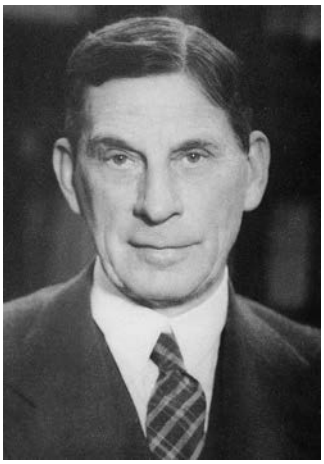


Figure 1.1. Ray Lyman Wilbur, M.D., President of Stanford University and chairman of the Veteran's Bureau Medical Council

Among the first issues facing the White Committee was the poor service received by Veterans. Three separate agencies—the Bureau of War Risk Insurance, the Public Health Service and the Rehabilitation Division of the Federal Board for Vocational Education—were involved, and often a single Veteran needed service from all of them. To address this problem, as the Committee's first task, members prepared and proposed an organizational chart that would put the three agencies under a single Bureau of Soldier Rehabilitation.[22]

Meanwhile, the American Legion, distressed with the problems faced by its members, had been campaigning for unification of the three separate Veterans' agencies. The lobbying effort seemingly had its effect on newly elected President Warren G. Harding who, shortly after taking office, appointed a committee of prominent citizens chaired by Gen. Charles E. Dawes to formulate a unification proposal. Members included Theodore Roosevelt, Jr., and representatives of the American Legion, the Red Cross, and labor, women's and government groups.[23] This committee accepted the White Committee's proposal almost without change. Its recommendations to President Harding became law in August 1921 with establishment of the Veterans' Bureau.[24, 25]

The Veterans' Bureau

While the new agency assumed all the responsibilities of the Bureau of War Risk Insurance and the Rehabilitation Division, at first it did not have responsibility for sick and injured Veterans. This was resolved about 8 months later, in April 1922, when President Harding issued an executive order that turned over to the Veterans' Bureau all 57 Public Health Service hospitals, which by then were primarily serving Veterans. Later, new Public Health Service hospitals funded under the first Langley Act were also transferred to the Veterans' Bureau.[26]

The high hopes for these reforms were quickly steered off course as the new Veterans' Bureau became plagued with problems. Waste, fraud and mismanagement during its first two years were brought to light in extensive 1923 Congressional hearings[27] that raised charges against the Bureau's first director, Charles R. Forbes, a personal friend of President Harding.

Figure 1.2. Charles R. Forbes, first Veterans' Bureau Director (1921-1923)

In September 1921, Forbes had "summarily dismissed" the Bureau's first Medical Director, Haven Emerson, M.D., a distinguished physician detailed from the Public Health Service to the Veterans' Bureau, which had no doctors on its staff.

Figure 1.3. Haven Emerson, M.D., first Veterans' Bureau Medical Director (1921)

Emerson publicly stated that the Bureau was "being made the football of politics" and that "plumbers and policemen" were "being substituted for scientific medical men."[28] In a talk in Columbus, Ohio, Emerson charged that $500,000 was being used for political patronage. Forbes maintained that this charge was false. He told Emerson that "his services were no longer desired," and replaced him with Col. R.U. Patterson.[29]

Figure 1.4. Robert U. Patterson, M.D., Veterans' Bureau Medical Director (1921-1923), later a member of the Medical Council

In February 1923, at the request of President Harding, Forbes was forced to resign after he was found to be selling government property to a business associate.[30] Congressional hearings in October and November of that year brought out evidence against Forbes so serious that the Justice Department later took up the case, resulting in prison terms for Forbes and one of his business associates.

With this tumultuous beginning, the new agency sorely needed a leader who was above reproach. Harding's choice was Gen. Frank T. Hines, a Veteran of the Spanish-American War and World War I. Hines, whose first job was to investigate the scandals and clean up operations, worked rapidly to improve service and lessen political control over the Bureau.[31] He set in place systems of controls and supervision that, in some cases, persist today.

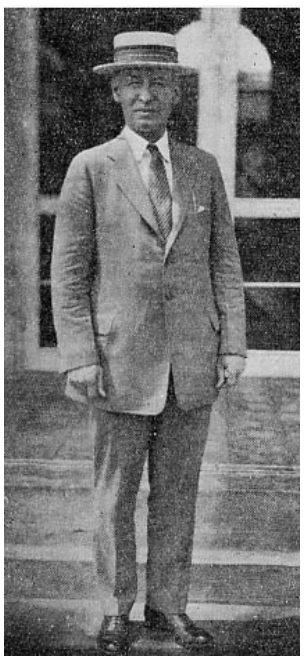


Figure 1.5. General Frank T. Hines, Veterans' Bureau Director (1923-1930) and Administrator, Veterans Administration (1930-1945)

Compensation vs. Care

Of the benefits to Veterans provided by the 1917 law, the two that fell to the new medical department of the Veterans' Bureau were establishing ratings for monetary compensation for disability and death, and providing medical care. Both compensation and care were complex new assignments and, in the immediate post-war years, compensation received the most attention. Compensation was most familiar to the Congressional overseers of the new Bureau because, like the old pension system, compensation decisions could be sensitive to political influence. Under Forbes, such influence had been a major problem. Although the 1923 Congressional hearings sought ways to improve Bureau performance in all regards,[32] more attention was paid to issues of compensation than to quality of medical care. While hospitals and dispensaries were finally in place, testimony at the hearings made clear that determining a Veteran's degree of compensable disability was their primary focus.

Lester Rogers, M.D., who had become the Bureau's Medical Director in May 1923 when Patterson was recalled to the Army, expressed concern in his testimony about medical care in the veterans' hospitals. Nevertheless, the Senators and their staff interrogated Rogers at length, and with considerable criticism, about his compensation decisions. There was little apparent interest in his complaints that he had insufficient authority to inspect the hospitals, or that many of their beds could not be used because of some hospitals' location or poor condition.[33] In January 1924, soon after the hearings concluded, the frustrated Rogers requested, and received, transfer to the New Haven (Conn.) Veterans' Hospital.

Figure 1.6. Lester B. Rogers, M.D., Veterans' Bureau Medical Director 1923-1924

Other testimony during the hearings cited instances of hospitals crowded with patients who could have been discharged except for their disability status. Because hospitalization itself was considered evidence of disability, a Veteran's compensation payment often decreased upon discharge, so the motivation to recover was lessened.[34] Yet despite pressures on physicians and staff at the hospitals to place emphasis on administrative efficiency, good medical care was also expected.

Advisors to the medical department

Even with the emphasis on compensation issues, one of Gen. Hines's main interests, once he had cleaned up the scandals and increased efficiency, was to improve the quality of medical care in the hospital system inherited from the Public Health Service. One of his first needs was for a new Medical Director to replace Rogers. In seeking a new permanent Medical Director for the Bureau,

Hines sought advice from prominent physicians, including Dr. Wilbur, who in addition to being President of Stanford University, was also President of the American Medical Association.[35] In April 1924, as a result of his search, Hines chose Edgar O. Crossman, M.D., a New Hampshire psychiatrist and Professor of Psychiatry at the University of Vermont, who had also been active in politics. Dr. Crossman had served in both houses of the New Hampshire legislature and as Federal Collector of Internal Revenue for northern New England. He had been President of the New Hampshire Medical Society and, more recently, New England District Manager for the Veterans' Bureau.[36] It is likely, judging by rapid progress in upgrading medical care after his appointment, that his recruitment included agreements about increased authority for the medical department and measures to increase quality.

Figure 1.7. Edgar O. Crossman, M.D., Medical Director, 1924-1926, 1928-1929

Hines had laid the groundwork for Crossman's mission in earlier contacts with Wilbur that included requests to nominate appropriate physicians to serve as "Special Consultants" to the Veterans' Bureau[37] and asking Wilbur himself to "act in an advisory capacity to the Veterans' Bureau when called upon on medical matters pertaining to your specialty." Hines's targets were specific:

> "It will be desired from time to time to obtain from you and from other members of the Consultant Board in General Medicine and Surgery, recommendations and advice concerning plans for construction and operation of general medical and surgical hospitals; the application of clinical methods of examination and treatment in hospitals, dispensaries and out-patient services; the question of medical follow-up care; and the questions of rating, for compensation and insurance purposes and for vocational training, of disabilities arising from general medical and surgical disabilities."

Hines further explained that the government was restricted in its ability to compensate adequately for expert advice, but that "it is confidently hoped that your deep and scientific interest in the problems of Veterans' relief, will prevail upon you to accept this request of the Bureau." Payment of railroad and Pullman fares and incidental travel expenses, plus a $20 daily fee, were offered.[37]

The Medical Council

Other advisors were also recruited, and, on July 22-24, 1924, 18 of the 22 members appointed to the "Council on Medical and Hospital Affairs" assembled for their first meeting in the Veterans' Bureau Central Office in Washington, D.C.[38] (originally built to house the Bureau of War Risk Insurance, this building has been continuously occupied by federal Veterans' agencies and today is the headquarters of the Department of Veterans Affairs). At its first meeting, the group modified its name to the "Medical Council of the Veterans' Bureau," and asked that its members be called "Councillors." The Council suggested additional members with needed expertise and formed committees for Tuberculosis, Neuro-psychiatry, General Medicine and Surgery and for "Hospitals, Dispensaries and General Medical Welfare." On the second day of their meeting, they met with President Coolidge.[39]

The Medical Council members were distinguished in their spheres of professional activity and leaders in academic, public and private medicine (Appendix IIb). Most of them were listed in *Who's Who in America* and held prominent positions in important medical organizations, including the American Medical Association, American Hospital Association, American Public Health Association, American College of Surgeons, American Psychiatric Association, National Tuberculosis Association and the American Heart Association. They held prominent university and government appointments and edited important journals. While no record exists describing how the original members were selected, a number of them had previously been advisors to the Veterans' Bureau or the Public Health Service. Appointments were permanent and subsequent Council members were recommended by the Council itself to add balance or replace those who had resigned or become inactive.

Although not present for the first meeting, Dr. Wilbur was elected to be Permanent Chairman. Wilbur had been one of the first Professors of Medicine and later Dean of the Cooper Medical College of Stanford University. In 1929, Wilbur became Secretary of the Interior in the Hoover administration, but he continued on the Medical Council while Lewellys F. Barker, M.D., from Johns Hopkins University became the Chair. Barker was William Osler's successor as Chairman of Medicine at Johns Hopkins, a position he held from 1905 to 1913. He established research laboratories as integral parts of the university's Department of Medicine, an unprecedented marrying of research and clinical practice.[40] Barker later played an active role in the Washington, D.C., Diagnostic Center (Chapter 2).

Figure 1.8. Lewellys F. Barker, M.D.

At the first meeting of the Medical Council,[41] a major concern expressed by the Bureau's Central Office medical staff and Council members was placed on the agenda, labeled "Medical Personnel - Status as to Rank and Pay." The subject was summarized for the record as follows:

> "As the Bureau's medical activities will last for 60 to 75 years for world war Veterans alone, should the medical officers have a permanent status offering continuous service, automatic and regular promotion which will assure young men a future, in which independent professional opinion and action can be exercised, or have a Civil Service status with lower pay, fewer allowances, and be subject to alterations of pay and the exclusive control of political superiors with each change of administration or oftener; average age of applicants for Civil Service jobs, 54 years."[42]

At the time, Bureau physicians in fact received less pay and had lower status than their colleagues in the Public Health Service or the armed services. At its first meeting, the Medical Council recommended the legal establishment of a Medical Corps for the Veterans' Bureau, that would be comparable to those in the other federal medical services. In the years following this first discussion, the Council spent considerable effort trying to get such a law passed,[43] but to no avail. Only after World War II was a VA Medical Corps created when Public Law 293 of 1946 established the Department of Medicine and Surgery.[44]

Other ways of improving the Veterans' Bureau hospitals as places for doctors to practice were suggested by staff and endorsed by the Council, including the establishment of systematic programs of instruction, such as the neuropsychiatric and tuberculosis schools already started on a pilot basis, and creating medical reference libraries in all hospitals and clinics. The Medical Council endorsed these concepts at its first meeting and came up with its own, more ambitious ideas to improve the quality of the professional staff and medical services. These included:

- Establishing a system of diagnostic beds for the evaluation of problem cases.
- Publishing a journal.
- Initiating a research program.

Hines and Crossman quickly accepted these innovative concepts in principle. And by the time the Council met for the second time four months later, planning for their implementation was well under way.

At its November 1924 second meeting, which became known as the "Cure-better-than-Compensation Conference," the Medical Council addressed a major philosophical question that had been problematic in providing federal Veterans programs. Wilbur addressed the group with this challenge:

> "If there is anything in this Medical Council, it seems to me it should come from the direction of the application of modern medicine to the problems of these men considered from a standpoint of curative medicine.... It seems to me that we must shift from compensation, and think in terms of repair and cure instead of in terms of how much damage has been done ... Let us see what we can do from the medical standpoint of harmonizing the out-patient with the

> hospital service to get the whole thing going as a medical concern, which will have the point of view of cure and attention instead of compensation and disability."[45]

The Council's Committee on Investigation and Research expressed the same concept, stating that a research program is "all the more called for by the recent shift in emphasis from administration to treatment as the primary objective of the Bureau."

Making the transition from a hospital system that primarily "warehoused" the disabled to one that focused on "cure" was to be a gradual and incomplete process. But along the way there were signs that the movement had taken hold. For example, Wilbur wrote in a 1924 site visit report that the Palo Alto Veterans Hospital appeared to be a well-run neuropsychiatric hospital with the latest equipment, advanced clinical laboratory and radiology facilities. Wilbur described the wards as "cheerful" and said that "The whole aspect of the hospital is one of cheer and hopefulness as compared with the ordinary institution of the sort." He also commented that the Chief of the laboratory "has an instinct for research."[46] On the other hand, there undoubtedly existed less favored veterans' hospitals that never reached excellence during this early period. Nevertheless, the most important contribution of the Medical Council was to help the Veterans' Bureau leaders focus on curative medicine as an important and laudable goal.

Michael Davis, M.D., a Medical Council member who was an authority on outpatient care, described the transition from "compensation" to "cure" after his 1926 inspection of some Veterans' Bureau outpatient facilities:

> "The work of the bureau physician for ambulatory cases was originally conceived chiefly as an aid in determining the compensation to be allowed the Veteran. The importance of thorough medical treatment has come forward more recently as the important element in bureau policy."[47]

Also in 1926, Winthrop Adams, M.D., of the Bureau's Central Office Medical Service described this change of focus to readers of the *Medical Bulletin*:

> "Regardless of the fact that all of us who have been connected with this work...have realized that more could be done in the way of applying medical knowledge to the cure or relief of Veterans' disabilities, it has, nevertheless, been apparent to all of us that the compensation feature was the paramount issue.... However, it is extremely gratifying to note that a decided change has taken place in this respect during the past year or two ...."

Adams credited the Medical Council for this change, saying:

> "The Bureau has had for the past two years recourse to the advice of a body of eminent physicians, which is known as the Medical Council... The Council has at each of its conferences insisted that the Bureau must accomplish more than it has in the past from the curative or therapeutic side."[48]

Introduction of a research concept for the Veterans' Bureau

At its first meeting in July 1924, the Medical Council appointed ad hoc committees to review member-proposed resolutions. One such resolution was presented by H. Kennon Dunham, M.D., a tuberculosis expert from Cincinnati who recommended that the Veterans' Bureau establish a medical research effort. The Chair of the ad hoc committee appointed to review and formulate this resolution was Louis Dublin, Ph.D., Vice President of the Metropolitan Life Insurance Company and a pioneer in the development of population statistics, who commented that the "statistical equipment of this Bureau, excepting that of the Census Bureau, is probably the largest in the Government."

Figure 1.9. Louis I. Dublin, Ph.D.

Dublin's committee proposed an ambitious resolution, which the Council discussed at length. Members were divided about whether they should add a new formal "Group on Investigation and Research" to their committee structure. Some were uncertain about the proposed research mission of the Bureau. The Group on Tuberculosis recommended "adequate research should be planned in connection with tuberculosis." All members saw the need for "statistical investigation," but some members questioned what could be done in clinical research. Eventually, the Council established a permanent Group on Investigation and Research and passed the following resolution to be forwarded to Gen. Hines:

> "The Committee unanimously agrees that the Veterans' Bureau should emphasize at every point the opportunity for investigation and research. This, because of the magnitude and importance of the work of the Bureau, and especially because of the field in which the work of the Bureau lies. Medical science is preeminently one in which investigation and research are called for. It therefore recommends:
>
> "1. That an office for investigation and research be established around the existent Division of Costs and Statistics.
> 2. That a permanent committee of the Council be appointed to formulate lines of investigation and research and which shall act as liaison for such work between the Bureau on the one hand and the medical profession on the other.
> 3. That problems of investigation and research shall cover:
> a. Those that arise directly from the administrative needs of the Bureau
> b. Those that arise through the clinical and laboratory care of patients

c. Those that will add definite contributions to medical knowledge

4. The Committee further recommends that it should be the policy of the Bureau, with the guidance of the Council Committee, to develop active relations and exchanges of material with various accredited research agencies throughout the country.
5. It further recommends that the results of such investigations as the Bureau may undertake, either under its own auspices or through the cooperation of outside agencies, be published in a bulletin of the Bureau, which may be issued either monthly or quarterly.
6. It recommends that the medical staff of the Bureau should be encouraged in every way to participate in the field of investigation insofar as immediate duties will permit such participation.
7. The Committee urges that the Bureau make every effort to obtain autopsy records through cooperating with local hospitals in order to improve its record of deceased cases in its files.
8. The Committee will further examine the work of the Division of Costs and Statistics, and will make, later, a report specifying the most pressing investigations which should be undertaken at once.

"The Committee recognizes the enormous scope of the field of investigation and research which the Bureau might properly undertake. On the other hand, it is felt that many difficulties will be encountered of a legal and financial character which might put great difficulties in the path of the entire program unless the field of investigation were narrowed somewhat to include, at the beginning, only those items of investigation which directly bear on the welfare of the men for whom the Bureau is responsible."[49]

A second resolution put forward by the Medical Council at this first meeting recommended establishing "regional diagnostic groups, consisting of the best available Bureau and local medical personnel, utilizing so far as possible, as consultants, members of this Council..." The Council recommended that patients with doubtful diagnoses be referred to these groups and that the consultants be adequately compensated.[50] This resolution led to the establishment of several Diagnostic Centers (discussed below) that contributed to the research program through the 1920s and 1930s.

The resolution about Diagnostic Centers also obliquely recommended affiliation with medical schools: "It is further suggested that where teaching institutions are available their use for this purpose will furnish excellent opportunity for the development of the attached Bureau officers as expert diagnosticians." Another committee of the Council, the Neuropsychiatric Committee, also favored affiliation with teaching institutions: "It is recommended that in the planning of future neuropsychiatric hospitals of the Veterans' Bureau, that are to be located in or near medical teaching centers or areas of large population, that certain of these be constructed and operated so that they may serve as teaching centers or schools for the medical personnel of the Veterans' Bureau."[51] Despite these recommendations, no formal affiliations between veterans' hospitals and medical schools occurred until after World War II.[52] The early VA research program had little or no formal input from academia except through the members of the Medical Council.

Before the second meeting of the Medical Council in November 1924, its membership was expanded by nine new members, four of whom, Albert E. Cohn, M.D., Allen K. Krause, M.D., Horatio M. Pollack, M.D. and Joseph W. Schereschewsky, M.D., joined Drs. Louis Dublin and Michael Davis

to form the Group on Investigation and Research. Davis left the Council in 1927, but the other five men continued as active advisors to the research program through the life of the Council. This enrichment of the Council's research expertise by adding four new members with research interests was consistent with Dublin's professed enthusiasm and the support of research attributed to Dr. Crossman and his staff.[53]

At this second meeting, the newly formed Group on Investigation and Research met and prepared an extensive report in which they referred to "enthusiasm for scientific work... from the Medical Director down...." They made the following recommendations:

> "1. The establishment of a Section on Investigation and Research in the Medical Service.
> 2. The appointment of a Director of Research ... This Committee shall act as advisor to the Research Director.
> 3. The Director of Research shall survey the present condition of the records kept both in the Bureau and in the field to determine their adequacy for the purposes of investigation....
> 4. The Director of Research shall investigate the standards and definitions for the clinical routine in hospitals, clinics and laboratories, and shall investigate the standards of diagnosis and treatment in the various establishments.
> 5. He shall have authority to study the work of all hospitals and other establishments of the Bureau.
> 6. He shall make plans for revision of the rating schedule.
> 7. He shall institute a study of the future hospital needs of the Bureau in cooperation with the Federal Board of Hospitalization.
> 8. He shall be responsible for the study of the clinical material available in the hospitals, clinics and out-patient departments of the Bureau, and emphasis shall be placed on the results of various methods of treatment.
> 9. ... The Research Director shall hold conferences with the medical officers at regular intervals to discuss medical problems and the results of the investigations conducted at the several hospitals. The staffs shall be encouraged to engage in research work in so far as their duties will permit, and favorable notation shall be made on the record of such medical officers as produce useful research work.
> 10. The Bureau shall arrange for the publication of a Monthly Bulletin, which shall be the medium for the publication of the studies made by the medical staff and the Research Director."[54]

The duties described for the Research Director represented an ambitious agenda for a single individual. The committee appears to have included functions they were sure the Bureau leadership wanted in order to persuade them that they needed a Director of Research. Nevertheless, it spells out what the committee, influenced by its two statistician members, thought of when they referred to research. Statistical studies of Bureau activities, systematically performed so that useful conclusions could be drawn, were related directly to Dublin's positions and expertise at Metropolitan Life. Adequate patient records were seen as essential to such studies, as well as to clinical research. Furthermore, standardized procedures were important not only to assuring quality control in patient care but also to acquiring usable data for clinical outcome studies.

The provision for research by clinical staff contained in the recommendations suggests that not much was expected of them. There was no provision for freeing clinicians' time to allow them to conduct the suggested research, and this limitation undoubtedly limited the growth of such endeavors.[55] Nevertheless, research projects in the hospitals and dispensaries did materialize.

By the time of the third meeting of the Medical Council on February 27-28, 1925, a section on Medical Research in the Bureau's central office had been formally established and recruitment for a Director of Research was under way. The Group on Investigation and Research advised the following qualifications for this Director:

> "1. He should be a physician familiar with Bureau procedure, and preferably one of the medical officers of the Veterans' Bureau.
> 2. He should have a good general and medical education.
> 3. He should have shown unusual interest in study and research and given some evidence of this interest in published work.
> 4. He should be a man in vigorous health and preferably under 45.
> 5. He should have unquestioned administrative ability.
> 6. He should be a man of personality, having the respect of the medical personnel of the Bureau."[56]

Other related progress was also under way in early 1925. A Diagnostic Center had been established in Cincinnati and one was in preparation for Washington, D.C. The first issue of the Veterans' Bureau *Medical Bulletin* was published in July 1925. Considering the many impediments to change, the speed of these events testify to the energetic efforts by Dr. Crossman and his staff, as well as Gen. Hines' decisiveness.

References

1. Jones, R.S., *The History of the American Legion.* Indianapolis and New York: The Bobbs-Merrill Company, 1946, 123.

2. Crossman, E.O., "U.S. Veterans' Bureau Hospitals." *Mod Hosp*, 1926. 26: 30-32.

3. Griffith, C.M., "The Medical and Hospital Service of the Veterans' Administration." *Military Surgeon*, 1936. 79: 251-267.

4. White, W.C., Billings, F., Bowman, J.G. and Kirby, G.H., *Report of the Consultants on Hospitalization Appointed by the Secretary of the Treasury to Provide Additional Hospital Facilities under Public Act 384 (Approved March 4, 1921).* Washington, DC: U.S.Government Printing Office, 1923, 1.

5. Furman, B., *A Profile of the United States Public Health Service*, DHEW Publication No. (NIH) 73-369. Washington, DC: U.S. Government Printing Office, 1973, 20.

6. Skocpol, T., *Protecting Soldiers and Mothers.* Cambridge, MA and London, England: The Belknap Press of the Harvard University Press, 1992, 107-130.

7. Leigh, R.D., *Federal Health Administration in the United States.* New York and London: Harper & Brothers Publishers, 1927, 314.

8. Adkins, R.E., *Medical Care of Veterans.* Washington, DC: U.S. Government Printing Office, 1967, 92-93.

9. Jones, *History of American Legion.* 1946, 125-126.

10. Leigh, *Federal Health Administration.* 1927, 168-169.

11. Adkins, *Medical Care of Veterans.* 1967, 102-103.

12. Leigh, *Federal Health Administration.* 1927, 172-174.

13. Rosen, G., *The Structure of American Medical Practice, 1875-1941*, Philadephia: University of Pennsylvania Press, 1983, 43-48.

14. Lewis, B.J., *VA Medical Program in Relation to Medical Schools.* Washington, DC: U.S. Government Printing Office, 1970, 65.

15. Leigh, *Federal Health Administration.* 1927, 181-191.

16. White, *Report of Consultants on Hospitalization.* 1923, iii, 1-2, and 63-64.

17. Adkins, *Medical Care of Veterans.* 1967, 65.

18. White, *Report of Consultants on Hospitalization.* 1923, 7.

19. White, *Report of Consultants on Hospitalization.* 1923, 15-16.

20. Telegram from Frank Billings, M.D. to Ray Lyman Wilbur, M.D., written at Chicago, IL, May 27, 1921.

21. Telegram from Ray Lyman Wilbur, M.D. to William C. White, M.D., written at Palo Alto, CA, June 3, 1921.

22. White, *Report of Consultants on Hospitalization.* 1923, 9.

23. Jones, *History of American Legion.* 1946, 132.

24. Adkins, *Medical Care of Veterans.* 1967, 110-112.

25. Leigh, *Federal Health Administration.* 1927, 200-203.

26. White, *Report of Consultants on Hospitalization.* 1923, 61.

27. *Investigation of the Veterans' Bureau: Hearings before the Select Committee on Investigation of the Veterans' Bureau, United States Senate, Sixty-Seventh Congress, October 22 to November 7, 1923.* Washington, DC: Government Printing Office, 1923

28. Leigh, *Federal Health Administration.* 1927, 207.

29. *New York Times*, New York, September 14, 1921, 19.

30. Smith, F.C., M.D., witness. "Testimony of Doctor Frederick Charles Smith." *Hearings Before the Select Committee on Investigation of Veterans' Bureau, United States Senate.* Washington, D.C.: Government Printing Office, 1923, 1: 651-664.

31. *Investigation of the Veterans' Bureau.* 1923, 755.

32. *Investigation of the Veterans' Bureau.* 1923, 10-150.

33. *Investigation of the Veterans' Bureau.* 1923, 790-791.

34. "Minutes of the Second Conference of the Medical Council with the Director and the Medical Director of the United States Veterans' Bureau." Washington, DC: U.S. Veterans' Bureau, 1924, 8.

35. Letter from Ray Lyman Wilbur, M.D. to Frank T. Hines, written at Palo Alto, CA, February 12, 1924.

36. Anonymous obituary, "Doctor Crossman." *US Veterans' Bureau Medical Bulletin,* 1929. 5: 647-648.

37. Letter from General Frank T. Hines to Ray Lyman Wilbur, M.D., written at Washington, DC, February 19, 1924.

38. "Minutes of First Conference, Medical Council, U.S. Veterans' Bureau, 22-24 July, 1924." Washington, DC: U.S. Veterans' Bureau, 1924, 16.

39. "Minutes of First Medical Council Meeting, 22-24 July, 1924." 1924, 34.

40. Harvey, A.M., *Science at the Bedside: Clinical Research in American Medicine, 1905-1945.* Baltimore and London: John Hopkins University Press, 1981, 64-70.

41. "Agenda of First Conference, Medical Council , U.S. Veterans' Bureau." Washington, DC: U.S. Veterans' Bureau, 1924, 14.

42. "Agenda of First Medical Council Meeting." 1924, 5.

43. Adkins, *Medical Care of Veterans.* 1967, 138-139.

44. Adkins, *Medical Care of Veterans.* 1967, 180 and pp. 209-211.

45. "Minutes of Second Medical Council Meeting, 10-11 November, 1924." 1924, 12.

46. Letter from Ray Lyman Wilbur, M.D. to E.O. Crossman, M.D., written at Palo Alto, CA, October 7, 1924.

47. Davis, M.M., "Improvement in out-patient service, with special reference to medical records." *US Veterans' Bureau Medical Bulletin,* 1926. 2: 108-112.

48. Adams, W., "The organization and administration of the medical divisions of regional offices." *US Veterans' Bureau Medical Bulletin,* 1926. 2: 113-117.

49. "Minutes of First Medical Council Meeting, 22-24 July, 1924." 1924, 23.

50. "Minutes of First Medical Council Meeting, 22-24 July, 1924." 1924, 14-15.

51. "Minutes of First Medical Council Meeting, 22-24 July, 1924." 1924, 21.

52. Adkins, *Medical Care of Veterans.* 1967, 215-218.

53. "Minutes of Second Medical Council Meeting, 10-11 November, 1924." 1924, 28.

54. "Minutes of Second Medical Council Meeting, 10-11 November, 1924." 1924, 29-30.

55. Ziegler, E.E., "Some properties of pneumocholin, a biochemical analysis." *J Lab Clin Med*, 1933. 18: 695-704.

56. "Minutes of the Third Conference of the Medical Council with the Director and the Medical Director of the United States Veterans' Bureau at Washington, D.C., 27-28 February, 1925." Washington, DC: U.S. Veterans' Bureau, 1925, 28.

(Intentionally Blank)

Chapter 2. The VA Research Program Before 1946

The year 1925 marked the effective transition from recommendation to action. The Veterans' Bureau leadership quickly grasped key initiatives that the Medical Council viewed as vital to strengthening this federal agency that had been thrust into the role of delivering health care services. A system of diagnostic clinics with links to outside consultants was established, and the *U.S. Veterans' Bureau Medical Bulletin* began publication as an important medium for sharing information. The formal establishment of a research component within the Veterans' Bureau that year was also a major milestone.

The advent of clearly identified medical research activity meant the marriage of projects and practitioners that had been informally at work with the type of hospital-based clinical research envisioned by the Medical Council. The Bureau's first Research Chief, Philip B. Matz, M.D., was an advocate of that philosophy and steered the agency's efforts primarily toward hospital-based inquiry directly related to the clinical conditions of a Veteran patient population.

In 1930, the most significant reorganization of federal Veterans programs to date occurred when President Hoover ordered a merger of three agencies to create the Veterans Administration (VA). The Veterans' Bureau, the Treasury Department's Bureau of Pensions, and the domiciliary system of National Homes were now under one umbrella that would endure as the government's largest independent agency for the next half-century.

By 1932, as the Nation's economy worsened, pressures were brought to bear on many government programs, including those serving Veterans. Provisions within the Economy Act of 1933 limited access to Veterans' hospitals for a time with revised eligibility criteria. Even though many restrictions were lifted as a result of public pressure, the VA still was burdened by the need to conserve funds. Some of Matz's initiatives toward centrally directed research were bogged down. With mounting demands for medical care, the Depression also forced some research-related programs such as the diagnostic clinics to provide direct forms of treatment. The monthly *Medical Bulletin* was reduced to a quarterly. Even the influential and highly regarded Medical Council was placed on an eight-year hiatus from 1931 to 1939.

The medical research climate of the 1920s and 1930s

What did the Medical Council members have in mind when they urged the Veterans' Bureau to launch a hospital-based clinical research program? Clearly, they were not thinking of what we now call "basic" medical research. Research facilities as we know them today did not exist in Veterans' Bureau hospitals, nor, for that matter, in most hospitals, even most of those affiliated with medical schools.[1] Erwin Chargaff later described the general climate of medical research in the United States in 1928 as "dominated by an unhurried, good-natured, second-rateness."[2]

Alfred E. Cohn, M.D., a member of the Research Group of the Medical Council, was the first editor of the *Journal of Clinical Investigation*. In its 1924 first issue, he wrote an introductory editorial on the purposes of medical research. He urged the mastery of the methodologies of physics, physiology, nosology and chemistry and asserted that the business of medical research "involves a legitimate interest in learning as well as a means for furthering the methods which lead to the cure of

disease."[3] While many authors in his journal focused primarily on the first aim, the basic understanding of medical problems, most of the early Veterans' Bureau authors, whether they published in the *Medical Bulletin* or in other journals, focused primarily on the second aim, seeking methods to cure disease.

As late as 1941, Alan Gregg, M.D., Rockefeller Foundation Director for the Medical Sciences, discussed his view of what constituted medical research.[4] He defined "research" as having "a flavor of dissatisfaction with the search made hereto, or with the hereto accepted explanations," and stated that "scientific research attains in its successful moments a constantly closer approximation to the truth." Like Dr. Cohn, Dr. Gregg divided research into two forms, observational and experimental. In his view, observational research (which covers most of the early VA research to be discussed in this chapter) requires that the investigator "bring so fresh and sensitive a mind to reexploration that the discoveries of exploration are possible." He admitted, however, that medical research is "often shot through with irregularities (and) intuitive guesses."

Support of medical research in the 1920s and 1930s came from researchers themselves and from foundations, universities, industry and, lastly, the government. Each of these sectors was represented on the Medical Council's Group on Research.

Foundations were the most important funders. From 1937 to 1940, American foundations' annual support of medicine and public health was estimated to be in the range of $12.2 to $13.5 million.[5] Foremost among the foundations was the Rockefeller Institute, founded in 1902. The Institute was the site of basic and clinical research in infectious diseases, cardiology and other prevalent medical problems.

The most prominent industrial support of medical research came from the life insurance industry, which was represented on the Medical Council and the Group on Research by Louis Dublin of Metropolitan Life Insurance Company, a major player in the public health movement. Dublin undoubtedly influenced the direction of the early Veterans' Bureau research toward demographic studies of a type that might be hard to reconcile with Dr. Gregg's definition of "true" research.

Probably the foremost medical school in support of research at the time was Johns Hopkins. Allen Krause, M.D., who directed a privately endowed laboratory there to study tuberculosis, was active in the Medical Council and its Group on Research.

A prominent player in governmental psychiatric research was St. Elizabeth's Hospital, the large federal psychiatric hospital in Washington, D.C., led by William Alanson White, M.D., also an active member of the Medical Council. The Public Health Service, which had long had responsibility for research on controlling infectious diseases, continued a program of intramural research in its Hygienic Laboratory.[6] The former Assistant Surgeon General for Research, Joseph W. Schereschewsky, M.D., was an active member of the Medical Council and its Group on Research.

With regard to governmental support, Dr. Gregg warned that: "The usual reservation regarding research under governmental control is that political preferment or unenlightened parsimony may

5

spoil the quality of the work."[7] And while these factors may have kept the VA research program small before 1946, the VA was not alone in receiving little governmental funding. As late as 1945, the National Institute of Health (as it was then known) spent only $3 million on medical research, while foundations contributed some $16 million.[8]

Before World War II, VA hospitals were not affiliated with medical schools, but this probably was not the key factor keeping the research program small. Only a few of the most prominent medical schools, especially those with full-time clinical faculty, had significant clinical research programs. The dilemma of most medical school faculty, likely shared by VA physicians, is described by Professor Harry M. Marks in his book, "The Progress of Experiment: Science and Therapeutic Reform in the United States 1900-1990":

> "Clinical investigators working in medical schools had to meet the demands of department chairmen to place service obligations before their research. As physicians, they faced competition from their medical colleagues for income, for patients to study, and for the allegiance of their students." In addition, "Outside of a few isolated research centers, few clinical specialists controlled the resources called for by their research programs."[9]

Important basic research, funded mostly by foundations, was being done at a few places, such as the Rockefeller Institute, the Mayo Clinic and a few medical schools,[10] but such studies were not expected of the Veterans' Bureau. Rather, the clinical research the Medical Council urged was closely associated with the patient. It endeavored to bring systematic observation and scientific method to bedside treatment.[11]

What did the VA mean by "Research"?

The Medical Council's view of research appropriate to the Veterans' Bureau emphasized standardization of practice and records and statistical studies. Members also emphasized the importance to the Veterans' Bureau of clinical research, particularly studies of outcomes. As Chairman Wilbur said in a 1926 address:

> "If we can get the best medical brains of this country concerned with the neuropsychiatric Veteran, not only to study him but to get him back 'on the job,' and also trace through over a period of years just what actually does happen, keeping alive a constant scientific interest in the problem, we will have done a real service in the advance of medicine."[12]

In 1926, Dr. Matz, Chief of Research at Bureau headquarters, described his view of that component of the agency's mission:

> "It must be clearly understood at the outset that research work in our service must show that upon consummation it will result in the betterment of the treatment of the beneficiary. It is not within the province of the Veterans' Bureau to carry on research work of a purely academic character; there are other governmental agencies for this line of endeavor; ours must be research based on practicability—something akin to the research work carried on by the large commercial corporations of the country. Our research work must eventually result in larger percentages of recoveries and reduced mortality rates of the beneficiaries of the United States Veterans' Bureau.

One of the functions of the research subdivision of central office is to guide and advise those research workers who are in need of help. The research group of the Medical Council has kindly volunteered to cooperate with the bureau in this important work and it is strongly urged that the personnel in the field avail themselves of this privilege and ask for advice when in need of it."[13]

Review of clinical research in 1926

An idea of the state of American clinical research in 1926 can be drawn from the published medical literature for that year. An examination of such journals as the *American Journal of Psychiatry,* the *American Review of Tuberculosis* and the *American Journal of Syphilis,* as well as the general medical journals *Journal of the American Medical Association, the Journal of Clinical Investigation, the American Journal of the Medical Sciences* and the Veterans' Bureau's own *Medical Bulletin,* reveals the types of studies that were attracting attention.
Most authors publishing in these journals were practicing physicians. There were many papers from the more prestigious medical schools and private hospitals, especially in the *Journal of Clinical Investigation*. Nevertheless, a substantial number of authors reported research conducted in their private practices or in hospitals and public institutions without academic affiliations.

Table 2.1 displays the types of reports published in these journals in 1926. These varied considerably among the journals. Of the journals reviewed, only the *Journal of Clinical Investigation,* then a quarterly journal in its second year, published a substantial amount of work on the pathophysiology of human disease—on topics such as the effect of hypothyroidism on plasma volume in patients, with repeat studies as the patients improved serving as the controls.[14]
"Preclinical" studies, experimental studies on normal animals or human subjects, appeared in most of the journals reviewed but made up a substantial proportion of studies only in the *Journal of Clinical Investigation* and the *American Review of Tuberculosis*. All of the journals reviewed, except the *Journal of Clinical Investigation,* published "interpretation and synthesis" papers presenting generalizations from personal experience or from review of the literature, with little or no new objective data.

Table 2.1. Comparison of articles published in medical journals, July-December, 1926

Subject matter covered	Percent of pages in original articles						
	Med Bull	JAMA	AJMS	JCI	AJSyph	AJPsy	AmRevTbc
Diagnostic methods	7	6	10	9	14	0	14
Population statistics	7	1	2	0	0	0	30
Descriptive studies	39	30	57	12	39	31	10
Therapeutic interventions	15	19	6	8	7	44	4
Interpretation and synthesis	32	37	18	0	33	25	18
Preclinical and pathophysiology	0	7	6	71	7	0	25
Total	100	100	100	100	100	100	100

While some coverage of therapeutic interventions was given in all of these journals, such interventions were emphasized in the *American Journal of Psychiatry* more than in the others. There were no reports of the prospective, randomized, placebo-controlled studies commonly seen today. Any studies that employed untreated controls were sequential, either comparing the patient's condition before and after treatment or showing the outcome in a series of untreated patients from previous years compared with the treated series. Randomized studies with untreated controls were

rare at the time. Even the later work of the prestigious Cooperative Clinical Group[15] did not meet this standard. In searching for the best treatment for syphilis, the Group presented standardized clinical statistics rather than controlled comparisons, despite a commitment to rigorous therapeutic investigation.

Population statistics were prominent in the *American Review of Tuberculosis* and the *Medical Bulletin.*

Most prominent in the journals reviewed were careful descriptions of the authors' clinical experience with their own patients. Case reports of one or a few patients presenting with unusual conditions or unusual manifestations of disease were frequently published, as they are today. There also were frequent clinical series, generally presenting one practitioner's or one clinic's experience with a certain disease condition. Such reports reflect a carryover, which still exists in some areas, of the situation Marks describes: "Physicians accumulated knowledge of disease over the course of a long career, making age synonymous with expertise." [16]

When diagnostic methods were presented, they were generally descriptions or standardizations of methods, with little evidence of any attempts to objectively validate the diagnostic usefulness of these methods.

This research climate supported investigations by Veterans' Bureau practitioners. In a sense, each patient successfully diagnosed and treated was himself a research project. The major skills needed to contribute to the medical literature were careful observation of patients and systematic recording of findings. These were within the reach of whoever was motivated to apply them. In the early days, many in the Veterans' Bureau were so motivated.

Even before the Central Office's formal research initiative began, doctors in the Veterans' Bureau hospitals were already doing this type of research. The first survey of ongoing Bureau research in 1926 revealed a wide variety of projects of the types that could be done in a patient care setting (Table 2.2).[13]

Table 2.2. Problems under investigation in Veterans' Bureau hospitals in 1926.

1. Penetration of aniline dyes into the central nervous system of experimental animals.
2. Study of immunity by injecting iodine and feeding thyroid extract to guinea pigs.
3. Basal metabolic estimation in tuberculosis.
4. Influence of nasal conditions on neuritis, chronic bronchitis and pleurisy. Use of plumbi acetatis in acute edematous conditions.
5. Malingering test by radio for deafness.
6. Relation of malaria to paresis.
7. Use of x-ray in treating tonsils.
8. The sputum in cases of pulmonary spirochetosis.
9. Study of the treatment of encephalitis lethargica.
10. Empyema and its relation to tuberculosis.
11. Psychoneurosis as evidence of organic pathology.
12. Production of a serum for treatment of tuberculosis.
13. Constitutional effect of exercise on nontuberculous and tuberculous patients.
14. Pulmonary tuberculosis and gastrointestinal symptomatology.
15. Electrocardiographic studies of neurocirculatory asthenia, mitral stenosis and myocarditis.
16. Electrocardiographic studies of pulmonary tuberculosis.
17. Efficiency of stovarsol in treatment of amoebic dysentery.
18. Gastric secretion in cases of colitis.
19. Comparison of McLean's kidney function test with phenolsulphonephthalien.

20. The bacteriology of osteomyelitis.
21. Laboratory investigation of phenoltetrachlorphthalein test for hepatic function.
22. Comparison of Kahn precipitation with the complement fixation test of syphilis.
23. Statistics on patients showing positive serological findings but negative clinical histories and no manifestations of syphilis.
24. X-ray abnormalities of the sella turcica and their relations to sugar tolerance and basal metabolic findings.
25. Investigation of leukocytosis following epileptic seizures.
26. Treatment of neurosyphilis with tryparsamide and bismuth, sulpharsphenamine and bismuth, and malarial blood inoculation.
27. Therapeutic study of effect of intramuscular and intravenous inoculation of bacillus typhosus vaccine in encephalitis lethargica.
28. Effect of intravenous administration of hypertonic dextrose solutions in cases of encephalitis lethargica.
29. Method for correcting colloidal gold solutions.
30. Study of the etiological factors in the production of inadequate behavior through neuropsychiatric symptoms.
31. Use of mercurochrome and gentian violet in cases of encephalitis lethargica.
32. Tuberculosis urinary antigens and the production of specific immunity.
33. Calcium content in the blood of tuberculosis patients.
34. The effect upon the blood sugar of potassium oxalate when used as an anti-coagulant.
35. Index of x-ray films, showing the rate of incidence of tuberculosis in pneumonoconiosis.
36. Study of positive Wasserman cases to determine what per cent show parenchymal infiltrations of lungs which simulate tuberculosis but are negative clinically.
37. Relation of atrophy of testicle to mumps.
38. Influence of intercurrent attacks of pneumonia on the course and prognosis of tuberculosis.

Initiatives to implement the Medical Council's recommendations

Following the July 1924 Medical Council recommendations, the staff of the Central Office Medical Service of the Veterans' Bureau quickly started three key initiatives: a system of diagnostic beds where problem cases could be evaluated, an internal journal to communicate findings and information and a formal research program. These three mutually important steps were accomplished within the next year.

Efforts to bolster Veterans' health care: the Diagnostic Centers

The new Diagnostic Centers, centers of excellence within the hospital system charged with analyzing difficult diagnostic problems, were started in Cincinnati (Ohio) and Washington, D.C., in 1925 and in Palo Alto (Calif.) (Figure 2.1) in 1928. Each of these units had in-house medical staff and a "board of consultants" that included local leaders in various fields of medical practice. Some members of the Medical Council also participated in these Diagnostic Centers. Roy D. Adams, M.D. was the chief consultant at the Washington Center, which had 250 beds,[17] and Llewellys D. Barker, Ph.D., Allen K. Krause, M.D. and William A. White, M.D. were on the consultant staff.[18] Dr. H. Kennon Dunham directed the Cincinnati Center.[19] The Council Chairman, Ray Lyman Wilbur, M.D. played an active role in acquiring the Center for Palo Alto[20] and supervised the recruiting of its consultant staff.[21]

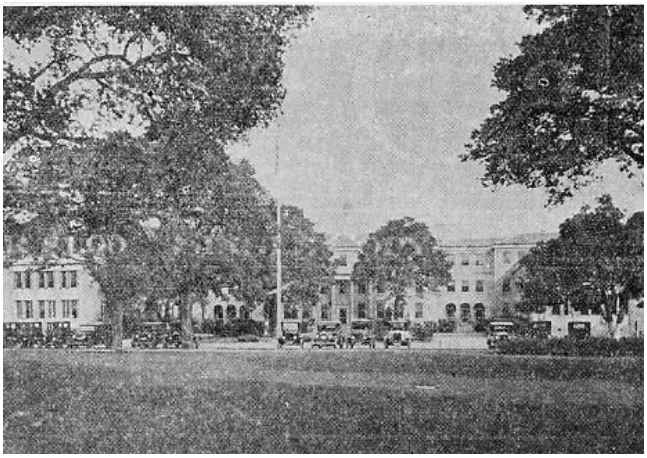


Figure 2.1. The Diagnostic Center at the Palo Alto Veterans Hospital, 1928

In 1929, the Palo Alto Diagnostic Center had 50 beds. In addition there were 50 beds in the same building for discharged Diagnostic Center patients who needed further treatment and another 50 beds for patients with other medical and surgical problems. The hospital also had several other buildings containing 860 beds for neuropsychiatric patients. The Diagnostic Center was equipped with a surgical operating suite, Ears, Nose and Throat (ENT) department, radiology department, laboratory, dental clinic and pharmacy. Its physician staff consisted of four generalists, four internists, a general surgeon, two neuropsychiatrists, an ENT specialist, a radiologist and a pathologist. In addition, 17 part-time specialists and nine consultants came from Stanford University and the University of California medical schools' faculties. Patients were examined by a number of physicians, given a spectrum of diagnostic procedures, and then had their cases reviewed in a conference. For example, a patient with gastrointestinal complaints would have gastric analysis, fluoroscopic x-ray series, barium enema, gall bladder x-ray, and multiple stool exams and blood tests.[22]

All physicians throughout the system were urged to transfer patients with complex problems to the Diagnostic Centers for workup and therapy recommendations. These Centers were credited with upgrading medical care in the Veterans' Bureau, and in 1929 the American Legion urged that new Centers be started in Boston and at the Mayo Clinic.[23] A fourth Diagnostic Center was established in Chicago in 1930 with Charles A. Elliott, M.D., of the Medical Council as "Dean of Consultants."[24]

As originally conceived, the Diagnostic Centers were not intended to carry out continuing treatment but to limit their role to diagnosis and specialized procedures. In the 1930s, the demand for treatment beds eroded this distinction. By 1931, many of the beds in the Palo Alto Diagnostic Center were used for routine treatment,[25] though there was continued demand for more diagnostic beds. In late 1934, the West Coast Diagnostic Center was moved from Palo Alto to the new VA hospital in San Francisco.[26] Ten doctors, 11 nurses, 30 other employees and 81 patients moved from Palo Alto to the new Diagnostic Center in San Francisco.[27] The Cincinnati Center, which was not connected to a VA hospital, closed some time after the opening of a large Diagnostic Center at the Hines VA Hospital in Chicago.[19]

Diagnostic Center staff were encouraged to do research, and they contributed to the general medical literature as well as to the *Medical Bulletin*. The Centers were well set up for case reports and record analyses as described in 1928 for the Washington, D.C., Veterans' Bureau Hospital:

> "A final copy of the final report on each case is forwarded to the records and research section, where all diagnoses and other pertinent data are indexed according to the scheme outlined in the August, 1928, issue of the *Bulletin*. The monthly and annual medical statistical reports are compiled and written up from the data assembled in this section. This section further serves as an aid in furnishing valuable data for the writing of medical papers."[28]

The *Medical Bulletin*

A key early recommendation of the Medical Council was that the Veterans' Bureau establish a journal. This publication, called the *United States Veterans' Bureau Medical Bulletin*, and later the *United States Veterans Administration Medical Bulletin*, was issued continuously from 1925 through 1944.

In the 1925 preface to the first issue, Dr. Edgar O. Crossman, the Medical Council's Medical Director, said:

> "*The United States Veterans' Bureau Medical Bulletin* is issued for the purpose of maintaining the high standard of medical service rendered claimants and beneficiaries of the bureau, by the collection and correlation of the experience of its medical officers in the diagnosis and treatment of their patients, and in the solution of their medical and administrative problems. It is also expected to promote research along practical lines and to present the results of study of the wealth of medical statistics contained in the records of the bureau. It is evident that the field for investigation is unlimited and that the opportunity to make helpful application of the conclusions is unprecedented."[29]

Especially as a monthly publication (until 1932), the *Medical Bulletin* was full of news of the Veterans' medical service, articles reflecting clinical experience, review articles and statistical studies. It included reports of original research by staff physicians. Even controversy and divergent opinions were encouraged.[30] It primarily published clinical papers, including many interesting case reports. There also were reports of carefully observed large patient populations and epidemiological reports using the database set up by the Research Subdivision. Every physician hired by the Veterans' Bureau was asked to submit at least one article for the *Bulletin* each year. Initially, about half of them did, and the editors chose from many submitted articles. In 1926 about 75 papers were submitted monthly for editorial review.[31] Many of the articles, particularly reports of unusual or difficult cases, were written by staff of the Diagnostic Centers.

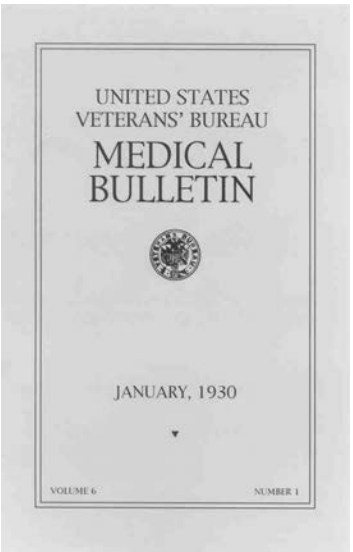


Figure 2.2. The *Medical Bulletin*, 1925-1944

The *Bulletin* served the Veterans' Bureau and Veterans Administration in much the same way as the American Medical Association was served by its *Journal*. Both journals allocated a large proportion of space to administrative matters, reviews, letters, editorials and meeting reports. Most of the original articles were based on authors' clinical experiences—either case reports, case series or teaching articles based on extensive experience. Some epidemiological and methodological articles appeared in both journals. Preclinical science played a very small role.

The scientific and medical subject matter of the *Bulletin* was closely aligned with Veterans' health care needs. Table 2.3 shows the distribution of topics in 1926, 1927, 1931 and 1935. There were many articles on treatment of patients with tuberculosis, unusual forms of tuberculosis, syphilis, both tuberculosis and syphilis, and psychiatric disorders, as well as reports of favorable results from innovative psychiatric treatments.

Table 2.3. Subjects of Articles in the *Medical Bulletin*, July-December, 1926, 1927, 1931 and 1935 (% of total pages)

	1926	1927	1931	1935
Tuberculosis	23.8	16.2	16.7	13.9
Neurosyphilis	1.9	4.1	6.8	5.6
Nonsyphilitic psychoses	8.0	12.8	8.0	5.6
Other psychiatric disorders	13.6	9.5	3.1	0.0
Neurologic (nonsyphilitic) disorders	8.3	0.9	2.7	3.0
Infectious diseases (other than neurosyphilis)	5.9	6.8	11.4	15.2
Neoplasms	8.0	2.5	20.1	11.4
Cardiovascular and arteriosclerotic disorders	11.5	9.7	6.3	6.1
Gastrointestinal disorders	2.9	7.2	2.7	2.5
Endocrine, renal, GU and arthritic disorders	8.8	5.2	9.0	11.6
Sequelae of trauma	2.4	3.2	2.5	4.0
Other	4.8	2.1	10.9	21.2

Physicians in the Veterans' Bureau were not the only contributors to the *Bulletin*. For example, librarians (who sometimes conducted "book therapy" for patients with mental illness), physical therapists, nurses and hospital managers also wrote articles. The *Bulletin* carried a news section, reporting activities of the Medical Council, items from Central Office and field hospitals, conferences at the hospitals, and Veterans' Bureau physicians' participation in other organizations' medical meetings.

The Central Office Research Subsection

The Medical Research Subdivision, which had been recommended by the Medical Council, became a reality when Philip B. Matz, M.D. (Figure 2.3), a pathologist, joined the Central Office as its Chief in September 1925.[32] He met with an enthusiastic Medical Council Group on Investigation and Research at the fourth Council meeting in October. They noted that Matz, who had been Chief of Laboratory Service at the Legion, Texas, Veterans Hospital, was selected from field hospital staff recommendations of people with the desired qualifications.

Administrative details of his appointment to Central Office were incomplete, so he was temporarily assigned to the Washington, D.C., Veterans Hospital. He had already:

> "a. Made a survey of the pathological laboratory of U.S. Veterans' Hospital #32, where he has been temporarily assigned.
> b. Installed a cross-index filing system for that hospital.
> c. Investigated apparently irregular blood findings of employees in the X-ray laboratory of the hospital and prepared a report on this study for publication in the *Bulletin*.
> d. Undertaken a survey of the facilities and personnel for investigation, and all research work now in progress in all Bureau hospitals.
> e. Got under way the standardization of the Wasserman test for all Bureau hospitals.
> f. Prepared and submitted to our Group a tentative working program for the Medical Research Division."[33]

Figure 2.3. Philip B. Matz, M.D., Chief, Research Subsection, 1925-1938.

The Medical Council Group recommended that the Division of Medical Research concentrate its first efforts on completing the survey of research facilities and on standardization of methods for diagnosis and treatment. Nevertheless, "in anticipation of future work," they stated that:

> "a. While the Chief of the Research Subdivision should foster and encourage all evidences of originality in the pursuit of research work, as a matter of policy, all projected studies should be submitted to him for approval. He should also recommend, at his discretion, to qualified stations in the field, problems for medical research.
> b. The Group is of the opinion that the Chief of the Division of Medical Research should install a system of regular progress reports on research work being carried out in the field.
> c. The Group believes it advisable for the Chief of Medical Research to keep in touch with selected medical schools and laboratories, so as to be in a position to locate suitably qualified research personnel, with a view to cooperating with the Civil Service Commission in filling existing vacancies in this line of work, or for acquiring new personnel for such activities."[34]

Philip Matz, M.D., Chief of the Research Subdivision

Dr. Matz was a 40-year-old pathologist from Baltimore, a 1908 graduate of the Long Island College of Medicine in Brooklyn. In 1909 he joined the staff of the Leavenworth (Kan.) National Military Home, where he was Chief of the laboratory until 1914. From 1914 to 1917, he was in private practice, conducting laboratories in Leavenworth and Kansas City and serving as consultant serologist to the Federal penitentiary at Leavenworth.

During World War I, Matz was Chief of the Laboratory Service at the Base Hospital, Camp Travis, Texas. In 1919, he published an extensive paper about the bacteriology of pneumonia in influenza victims. He reported that, on throat culture, Pfeiffer's bacillus (believed at the time to cause influenza) was present in 39 percent and pneumococcus in 10 percent of 868 patients with uncomplicated influenza. None of the blood cultures from patients with uncomplicated influenza was positive. In influenza patients with complicating pneumonia, on the other hand, pneumococcus was present in the sputum in 68 percent of 1,505 sputum cultures and Pfeiffer's bacillus in none of them. Of 178 blood cultures from pneumonia cases, 11 percent were positive, all with pneumococcus. Spinal fluid cultures in 16 cases of meningitis also all revealed pneumococcus of various types. He found acidosis and urea retention in the pneumonia patients, with acute parenchymous inflammation in the kidneys at autopsy.[35]

After the war, Matz joined the Public Health Service and was assigned as Chief, Laboratory Service, to a series of five Public Health (later Veterans' Bureau) Hospitals. During this period, he wrote an extensive clinical research paper on the calcium content of the blood in normal and tuberculous subjects. He established the normal range of fasting serum calcium in 50 normal subjects and showed that it was no different in 72 patients with tuberculosis. In both normal and tuberculous subjects, he demonstrated a modest increase in serum calcium after a high calcium meal or ingestion of inorganic calcium salts, an effect that increased when cod liver oil was given. He presented a few studies in both normal and tuberculous subjects showing an inverse relationship between serum calcium and the coagulation time.[36]

He had also taken postgraduate work at the University of Kansas, St. Louis University, Rush Medical School and the Rockefeller Institute for Medical Research.[37]

After Matz moved to the Central Office, he and his small staff continued to follow the guidance of the Medical Council's Group on Research. The staff concentrated on setting up a statistical system for tracking patients, which was necessary to understand the Bureau's medical care responsibilities better. Early publications were primarily statistical descriptions of the Bureau's patient population and used information gathered by the Evaluation Division in Central Office.

A 1926 study by Matz of cardiovascular disease among Veterans[38] currently hospitalized showed that 59 percent of the 537 such cases reported had valvular heart disease. Another 21 percent had myocarditis, a surprising finding that Matz attributed in part to the high incidence of tuberculous myocarditis. In a later report of 330 deaths due to cardiovascular disease during 1923-1925,[39] valvular disease was responsible in 47 percent and myocarditis in 28 percent of the fatalities. Average age at death was 34 years. "Angina pectoris" was listed as the cause of death in four cases, but "myocardial infarction" or its equivalent was not included as a cause of death.

Similar reports by Matz described the Bureau's patient populations with tuberculosis (6,715 inpatients);[40] degenerative diseases of the heart, blood vessels and kidney;[41, 42] and neuropsychiatric diseases.[43] The tuberculosis study reported a preponderance of moderately advanced cases (48 percent) and far advanced cases (44 percent). It demonstrated a poorer response to treatment among "colored" than among white patients, even when the stage of their disease was taken into account. The study of 4,020 cases of "degenerative diseases" included 306 patients with arteriosclerosis (local, cerebral, general or unclassified), 435 with cardiac hypertrophy and 3,279 with some form of nephritis. The study of neuropsychiatric diseases reported that 65 percent of 12,220 such Veteran patients suffered from dementia praecox (schizophrenia), and 6.4 percent from general paresis (tertiary syphilis of the brain). Comparing 4,313 Veterans' Bureau psychiatric admissions with 71,676 admissions to civilian mental hospitals, Matz found similar incidences of dementia praecox and general paresis, but that more patients with manic-depressive psychosis were admitted to civilian hospitals and more patients with nonpsychotic conditions were admitted to veterans' hospitals. A 1927 article reports the distribution of compensable disabilities among World War I Veterans.[44] Matz also published demographic reports on the Veterans' Bureau hospital activities monthly from October 1926 through March 1927.[45-49]

Dr. Matz's writings in the *Medical Bulletin*, as well as articles from field hospitals encouraged by him, were sprinkled with information about fever therapies for general paresis, a form of tertiary syphilis. In 1926, he reviewed recent publications about the procedure.[50] There followed in 1927 a report of early experience with malarial treatment at the Hines, Bronx, Augusta, Ga, Gulfport, Miss. and North Little Rock, Ark. Veterans Hospitals. Of 112 patients treated, 65 percent showed short-term improvement. Spinal fluid Wasserman became negative in only 28 percent, while the blood Wasserman became negative in 62 percent. This report concludes, "It is believed that the results obtained following this form of treatment justify its continuation and further development. While no rational explanation can be given of its mode of action . . . the effect may be attributable to certain indefinable alterations or reactions of the body."[51] A follow-up article reported on 179 cases, including 67 new cases. By that time, patients had been under observation for as long as 18 months,

and the results were "highly satisfactory": 72 percent were "improved" or "greatly improved" and 66 percent and 28 percent, respectively, had negative blood and spinal fluid Wasserman tests.[52]

In 1926, Matz also published in the *Medical Bulletin* review summaries of articles reporting autopsy findings in paretics treated with malaria. There was reversion of histology toward normal, compared with untreated, patients, and a lack of spirochetes in the brain tissues.[53] Matz included practical information about the procedure: a note about how to transport blood containing malaria plasmodia through the mail for use in patients at other hospitals.[54]

In 1928, Matz published an updated report of Veterans' Bureau experience, now reporting 346 patients treated with "inoculation malaria." This time, instead of the in-house *Medical Bulletin*, he published the Veterans' Bureau results in the *Journal of Nervous and Mental Diseases*. This report included a review of the current status of the treatment, extensively quoting the experience of civilian authors and comparing Veterans' Bureau experience with that of others. The Veterans' Bureau hospitals reported no mortality due to treatment, in contrast to about 5 percent mortality in other series. This was thought to derive from exclusion of high-risk patients and the relatively young age of Veteran patients. Among treated patients, 24 percent were greatly improved and 23 percent were improved, results comparable to other series. For comparison, Matz quoted the published incidence of spontaneous remissions from general paresis to be in the range of 3 percent to 10 percent.[55]

Other articles by Matz reported experience in treatment of paretic patients with ratbite fever (sodoku, due to spirochaeta morsus-muris, an organism that causes a malaria-like fever), with an early suggestion of improvement with less reported mortality than with malaria or relapsing fever.[56] Other reports reviewed clinical conditions and standardization of clinical and laboratory tests.[57-63]

In 1926, Dr. Matz and Dr. H.L. Gilchrist, Medical Director of the Army's Chemical Warfare Service, advised by the Medical Council's Drs. Allen K. Krause and H. Kennon Dunham, began to locate and study Veterans who had been victims of poison gases during World War I. In 1928, they presented a preliminary report,[64] in which they described the study and its difficulties. While the group wanted to study each of the gases separately, often several types of gas had been used together. There were a total of 70,742 U.S. gas exposure casualties in World War I. In only 37,025 of these was the type of gas known: chlorine, 1,843; mustard, 27,771; phosgene, 6,834; arsenicals, 577. Frequently, men who were gassed had other injuries, which could interact with gas effects. Of the 70,742 total gas casualties, 200 died on the battlefield and 1,221 died in field hospitals, a 2.01% early-death rate.

In 1921, the Army had reviewed the status of a sample of the casualties who had lived to be discharged from the field hospitals. Of the 3,431 cases reviewed, 353 (10.3 percent) were thought to have a gas-related disability in 1921. The long-term effects of gassing were unknown.

In a survey of the problem, Matz and Gilchrist contacted U.S. and international physicians who had wide experience in treatment of gas victims, asking for their opinions about late (eight to 10 years) effects. The results were not helpful: "An analysis of the opinion of the civilian clinicians as well as the army officers of this and of foreign countries was so at variance and so conflicting that a summarization would result in no definite conclusions. It was felt, therefore, that this difference of

opinions was sufficiently great to justify the present study of the residual effects of wartime gassing."[65]

The Veterans' Bureau study, carried out from 1926 to 1928, included a review of all deaths in the men reviewed by the Army in 1921, and a thorough clinical follow-up of those in the Army study believed in 1921 to have a possible gas-related disability. About 10 years after the initial gassing, they called the Veterans in for a thorough re-examination and review of their complete case histories.

The authors acknowledged that the selection method made impossible an overall statistical analysis of the late effects of wartime gassing, since those who showed no evidence of effects in 1921 were not studied in the 1926-1928 review. Rather, the authors sought to establish as unequivocally as possible in a select group those conditions that might be due to gassing. They found in some of the men infrequent but definite anatomic and clinical residua of the gassing, apart from other considerations. The most frequent effect was a chronic bronchitis with asthma-like features. Gassing did not appear to predispose to tuberculosis, but it did aggravate existing tuberculosis.[65-68] The results of this study are summarized in Table 2.4.

Table 2.4. Summary of results of the 1926-1928 Veterans' Bureau-Army study of the late effects of wartime gassing

Incidence of gas-related death or residual disability in 1926-1928 (eight to 10 years after gas exposure) among those surviving to leave the field hospital:

	Chlorine	Mustard	Phosgene	Arsenicals
Total number examined	96	89	79	43
Death	0.24%	1.48%	0.40%	0.87%
Residua	2.00%	4.41%	1.58%	0.73%
Death or residua	2.24%	5.89%	1.98%	1.60%

(Note that these incidence figures omit any casualties who had no evidence of gas-related disability in 1921 but who may have developed a disability after 1921.)

Gas related clinical findings in 1926-1928

	Chlorine	Mustard	Phosgene	Arsenicals
Chronic bronchitis	x	x	x	x
Emphysema	x	x	x	
Pulmonary tuberculosis	x		x	
Bronchial asthma		x	x	
Pulmonary fibrosis			x	
Pleurisy				x
Bronchopneumonia				x
Chronic conjunctivitis		x		
Corneal opacities		x		

Matz also published a follow-up study of Veterans who had developed mental illnesses while in the military.[69] This was of special importance because of the Veterans' Bureau's heavy psychiatric workload (Table 2.5). This study and its sequelae enriched the practical experience with psychiatric disease of VA doctors, who, by the middle 1930s, found that more than half of their patients suffered from neuropsychiatric diseases.[70] These doctors played an active role in setting up methods for psychiatric screening of inductees at the beginning of World War II.[71]

Table 2.5. Analysis of Veterans who were service-connected for neuropsychiatric disease

Military discharges for neuropsychiatric disease, 1917-1919: 78,930

Veterans hospitalized for neuropsychiatric disease

Year	Veterans' hospitals	Other hospitals	Total
1920	4,926	3,556	8,482
1928	13,057	1,620	14,677

Follow-up of selected patients admitted in the first half of 1922

1922 diagnosis	1928 status (%)			
	Improved	Unimproved	Died	Unknown
General paresis (neurosyphilis) (n=246)	15	1	72	0
Dementia praecox (schizophrenia) (n=843)	38	37	10	14
Nonpsychotic (n=609)	40	56	1	5

The Medical Research Division expanded modestly during the late 1920s. In his 1929 address to the Medical Council, Dr. Crossman said:

> "You will recall that the matter of research was discussed at the last meeting and we have, as a result of the recommendations which were made, authority to employ a cardio-vascular specialist to head up this part of the research department.…A medical statistician has been authorized, and we have in view, I think, a very good candidate for that particular position. However, we do need your assistance in securing the type of man we are looking for to handle the cardio-vascular work…."[72]

This expansion was transient, however. A 1934 report names only Dr. Matz and two assistants in the Research Subdivision.[73] In 1930, Dr. Matz reported of his own work that:

> "The following studies have been conducted by the Research Subdivision and papers have been prepared and published in various medical journals during the fiscal year:
> 1. A study of intestinal tuberculosis among ex-service men.[74]
> 2. The future incidence of nervous and mental disease among ex-service men.[75]
> 3. The Gerson-Sauerbruch regimen in tuberculosis.[76]
>
> "The following studies are now being conducted and will shortly be completed:
> 1. A clinical and statistical study of diabetes mellitus.
> 2. A study of malignancy among ex-service men.
> 3. A study of manic-depressive psychosis - to be presented at the Association for Research in Nervous and Mental Disease, December, 1930.
> 4. A study of the arthritides."

These studies were all later published,[77-85] as were studies of habit-forming drugs,[86] food poisoning,[87, 88] the coincidence of malignancy and tuberculosis,[89] the outcome of surgical treatment of tuberculosis[90] and the incidence of bronchogenic carcinoma.[91] In a 1932 report on dispensary care in the VA, Matz compared the outcome of VA clinics with those of other hospitals, showing that the VA outcome compared favorably. Of the patients discharged from VA clinics, 82 percent were considered to be cured or improved.[92]

In 1935, Matz published in the *New England Journal of Medicine* a series of five articles about heart disease in Veterans.[93-97] In 1937 and 1938, he published a series of articles about silicosis.[98-101]

Altogether, 89 publications from his time as Chief of the Research Subdivision were listed in the *Index Medicus*.

Figure 2.4. Philip Matz, M.D.

On June 1, 1938, Dr. Matz undertook a two-month tour of VA hospitals active in research. On June 28, he was in Los Angeles, where he held a conference on studies of tuberculosis. After the meetings, he and a group of VA colleagues went to the beach in Santa Monica, where he suffered a fatal heart attack at the age of 53.[37, 102]

Matz had been an active and creative leader. His assistant, Anne Bambery, wrote to his sister after his death:

> "I worked with Dr. Matz for about thirteen years and in that time I learned to know him as a very sincere counselor and friend. He was so kind and considerate of everyone."[103]

Horatio Pollack, Ph.D., statistician for the New York Department of Mental Hygiene, who was in the Group on Research of the Medical Council, wrote:

> "In connection with my work on the Medical Council of the Veterans' Administration, Dr. Matz and I became intimate friends. I had the highest regard for him as a man, as a physician, and as a research worker."[104]

Arthur Vorwald of the Trudeau Foundation, Saranac Lake, N.Y., wrote:

> "I shall remember Dr. Matz for his keen enthusiasm and vision so well displayed at the various round table discussions held in connection with the National Tuberculosis Foundation."[105]

After Matz died, there were no major new VA research initiatives until after World War II. The independent Research Subdivision in VA Central Office was merged with a section on postdoctoral training to form the "Postdoctoral Training and Research Division," headed by Hugo Mella, M.D. Mella was a neuropsychiatrist who, during his postdoctoral fellowship at Harvard, had published

basic and clinical neurological studies.[106-114] He had entered the Veterans' Bureau about 1926 and had held a variety of administrative positions. While he was Clinical Director at the Palo Alto VA Hospital and Manager of the VA hospital at St. Cloud, Minn., he had published a variety of clinically oriented and philosophical papers.[115-123] After he became Chief of the Postdoctoral Training and Research Division, he published only the results of a follow-up study on neurosyphilis that Matz had not had time to complete,[124] and a report of results of sulfapyradine treatment of 92 cases of lobar pneumonia.[125] Otherwise, his research activities were primarily supervisory, consisting of receiving monthly reports from the three designated research laboratories and arranging for their budgets and personnel. The vigorous leadership Matz had provided, reflected in acknowledgements in publications by VA doctors, had been lost. Pressures of funding, short staffing, and, later, wartime conscriptions took their toll. The small but vigorous research effort reflected in the *Medical Bulletin* dwindled.

Research in the hospitals

From the beginning, research was encouraged in the Veterans' Bureau hospitals, though until 1932 there seems to have been no organized effort to establish centrally funded laboratories specifically dedicated to full-time research. Earlier, the policy encouraging research led to many small investigations by hospital staff members.

Most of these were studies that could be done without specific funding. For others, the source of the money is unknown. Most likely, in the tradition of the time, the investigators funded their own research or used their ingenuity to adapt existing resources to research use.

An interesting series of studies on the effect of using bile salts to treat pneumococcal pneumonia was reported in the early 1930s by Edwin E. Ziegler, M.D., a graduate of the George Washington University School of Medicine, who entered the VA's Associate Physician program in 1929. This was a program in which about 20 young doctors per month were recruited straight out of internship and given a six-week training course before being assigned to a VA hospital.[126] Ziegler was assigned to the laboratory at Northport VA Hospital, where he probably worked under the guidance of Linneaus H. Prince, M.D., a pathologist whose name is connected with a variety of innovative research projects. Ziegler attended VA postdoctoral courses in pathology and later cited the VA as the source of his pathology training.[127]

In his first paper on the subject of bile acids and the pneumococcus,[128] Ziegler stated:

> "Since pneumococci are soluble in solutions of bile salts, my coworkers and I thought of using the bile salts themselves in the treatment of pneumonia. This paper deals with the treatment of pneumonia with the bile salts sodium taurocholate and sodium glycocholate, with some laboratory experiments on the salts and their properties."

Using in vitro studies, he showed that concentrations of bile salts that lyse pneumococci did not damage erythrocytes. He reported results in three patients, including one with meningitis, whose pneumococcal pneumonia improved after intravenous bile salts. However, the injections led to a sclerosing phlebitis.

Ziegler went on to study sodium dehydrocholate, which was less toxic to the veins and "can be given intravenously in quite large doses and in convenient concentrations without injury."[129, 130] He extended these studies when he was visiting the Army Medical School Department of Bacteriology, while taking a postgraduate course in pathology and bacteriology given by the Veterans' Bureau in affiliation with the Army Medical School.[129] His findings demonstrated an antipneumococcal action of the dehydrocholate, both in vitro and in animals, with minimal toxicity. He extended these studies to demonstrate immunity to pneumococcus in rabbits injected with a mixture of sodium dehydrocholate and pneumococci.

As seems to have been frequent in the early VA, Ziegler was reassigned several times during his tenure. He continued to study the sodium dehydrocholate-pneumococcus mixture, "pneumocholin", while working as a pathologist at the Coatesville, Pa., and Boise, Idaho, VA hospitals over the next few years. In 1933, he reported that pneumocholin caused no deleterious effects when injected intravenously and that it "induces a very effective immunity for between three and four days,"[131, 132] an effect that he felt would be useful in clinical practice because of the extended clinical time course in pneumococcal pneumonia.

Ziegler also devised a method for measuring the "oxygen absorbing power" from the ratio of oxygen consumption to respired volume, as measured with a basal metabolism device.[133, 134]

Another young physician, Justin J. Stein, M.D., from Texas via the Mayo Clinic, joined the tumor clinic at the Hines VA Hospital in 1935 as a member of the "X-ray, Radium Therapy and Surgery "section. He became certified in radiology in 1937. Publishing a series of clinical papers on the importance of early diagnosis and treatment of cancer[135] and on unusual tumors of the intestine,[136-138] Stein reported extensively on aspects of lung carcinoma, particularly cancers of the apex of the lung.[139-144] He later joined the Navy, but continued to report in the *Medical Bulletin* about his combat experiences.[145, 146] After the war, Stein moved to Los Angeles, where he became a faculty member at UCLA, a consultant at the West Los Angeles VA Hospital and Chief of radiation therapy at the Long Beach (Calif.) VA Hospital.[147]

A series of intriguing reports in early issues of the *Medical Bulletin* deal with the use of Mercurochrome intravenously in the treatment of bacterial infections. This approach had been started at the Brady Urological Institute at Johns Hopkins in 1922, when it was used to cure a man believed to be moribund from septicemia. In July 1925, C. D.Allen, M.D., from the Memphis Veterans' Bureau Hospital, published his experience with 100 cases in the first issue of the *Medical Bulletin*,[148] and added another 51 cases the following year.[149] He found the best results to be in infections of the genitourinary tract and in arthritis. Albert Martin, M.D.,from the San Fernando Veterans' Hospital (a southern California hospital later important in the VA tuberculosis trials) reported a case of hemolytic streptococcus bacteremia following empyema cured by intravenous Mercurochrome,[150] and R.L. Harris, M.D., from the Augusta (Ga.) VA Hospital reported similar success in a case of bacteremia due to streptococcus viridans.[151] H.E. Foster, M.D., from the Sheridan (Wyo.) VA Hospital reviewed the literature on this treatment in the *Medical Bulletin*, concluding that "In from 50 to 75 per cent of the cases treated it has been highly efficacious in single or repeated doses."[152] Mercurochrome was perhaps the most successful of the external disinfectants used internally, but its use was eventually abandoned.[153]

A major follow-up study of fractures of the long bones in World War I by J.B. Walker, M.D., a consultant to the Veterans' Bureau Regional Office in New York City, appeared in the *Medical Bulletin* in 1929.[154-157] Of 16,339 soldiers with one or more battle fractures of a long bone, 2019 (16.6 percent) died. Of 39,569 soldiers with nonbattle fractures, 1,346 (3.4 percent) died. Of the soldiers with long bone fractures, 4,178 (7.5 percent) had amputations, and 187 of those soldiers died. Osteomyelitis was a major cause of death and disability. The report details various types of fractures, treatments and outcomes.

While a large part of VA research during this pre-World War II period was carried out in coordination with the Central Office research unit or by the three designated Research Laboratories (below), VA professional staff continued to publish in the *Medical Bulletin* from its inception in 1925 until the beginning of the war. Table 2.7 presents a sampling of titles from the *Medical Bulletin* through these years, reflecting areas of interest of VA staff whose primary responsibility was patient care rather than research.

Table 2.6. Sampling of titles from the *Medical Bulletin* of articles written by clinicians in the hospitals, not in designated research units

1925:
Resume of treatment of 25 cases of diabetes mellitus with insulin.[158]
Residuals of encephalitis lethargica.[159]
The blood vessels in tuberculosis: some aspects of the part played by the blood vessels in the dissemination of tuberculosis.[160]
Treatment of Raynaud's Disease by negative pressure.[161]

1926:
A study of Larson's ring test applied to 315 cases of tuberculosis.[162]
Adenocarcinoma-primary in the renal tubules.[163]
A preliminary report on attempts at active immunization of guinea pigs by urinary antigens from cases of tuberculosis.[164]
Correlation of clinical and laboratory procedures in tuberculosis: 1. The complement fixation test.[165]

1927:
Studies on the bacteriocidal properties in vitro of certain fatty acids irradiated with the quartz-mercury-vapor spectrum.[166]
Report of cases of leprosy with unusual manifestations.[167]
Notes on amnesia.[168]

1928:
Thoracotomy for empyema complicating pneumonia - analysis of end results in 100 consecutive cases.[169]
Multiple sclerosis.[170]
Ancient Greek, Etruscan and Roman dentistry.[171]
A study of the emotions in psychotic patients (a report of the examination of 100 psychotic patients with the Pressey test).[172]
A comparative study of the Kahn and complement fixation tests of spinal fluid.[173]

1929:
Tetany from overbreathing.[174]
The Gregerson test.[175]
Julius Caesar, epileptic.[176]

1930:
Preliminary report of fifteen cases of Sodoku treatment of general paresis.[177]
Typhoid vaccine in the treatment of general paralysis of the insane.[178]
Narcolepsy.[179]
Value of media containing certain iron compounds in differentiating the typhoid-colon group of organisms.[180]
An improved method for staining tubercle bacilli in tissues cut by the frozen-section technique.[181]
Carbon dioxide-oxygen inhalations in catatonic dementia praecox.[182]

1931:
Experiments on bacteriophage adsorption by vulnerable bacteria.[183]

Medical science in the thirteenth century.[184]
The use of subarachnoid lavage and ethylhydrocupeine in meningitis.[185]
Stramonium in encephalitis.[186]

1932:
Bronchial spirochetosis, with report of a case.[187]
A world's record for the transportation of entamoeba histolytica.[188]
Elliptical human erythrocytes: report of two cases.[189, 190]
Observations of heart action under vagus stimulation.[191]
The incidence of syphilis in 5,000 Negro ex-service men.[192]

1933:
Intravenous administration of sodium amytal in acute psychotic episodes.[120]
Psychosis with alcoholic pellagra.[193]

1934:
An unusual case of hysteria with a retrocursive gait.[194]

1935:
Super-diathermy in the treatment of dementia paralytica.[195]
Nineteen cases of pneumonia in members of the Civilian Conservation Corps with no deaths.[196]
Brain abscess consequent to latent head trauma.[197]
Sulphur (colloidal) therapy in the treatment of arthritis.[198]

1936:
Effects of long hospitalization on psychotic patients.[199]

1937:
Use of benzedrine sulphate in catatonic stupors.[200]
Molokai and its leper colony.[201]

1938:
Hypoglycemic shock therapy in schizophrenia: results of treatment of six cases.[202]

1939:
Experience with the insulin shock therapy of schizophrenia.[203]
Bacteriological examination of eating utensils.[204]

1940:
Herpes zoster in early syphilis.[205]

1941:
The treatment of schizophrenia with desoxycorticosterone acetate.[206]
The status of thyroid ablation for intractable heart disease.[207]

Physicians in Veterans' Bureau hospitals received some recognition outside the agency and its *Medical Bulletin*. In 1927, seven Veterans' Bureau scientific and medical exhibits were included in the national meeting of the American Medical Association, in Washington, D.C. Included were exhibits on treatment of neurosyphilis with malaria or rat-bite fever, on laboratory findings in various psychoses and in syphilis, and on the effects of bran on gastrointestinal X-rays.

In 1930, progress reports from the Bronx (N.Y.) and Perry Point (Md.) VA hospitals were reported in the *Medical Bulletin*.

> "From the Bronx Veterans Administration Hospital:
> 1. "Sodoku treatment" for general paralysis given 19 patients between April 1929 and April 1930. Results: Some improvement, no deaths.

2. 12 paretics inoculated with tertian malaria blood. The malarial paroxysms were terminated by quinine. This treatment was followed by sulpharsphenamine. The patients were gaining weight and strength, and there had been no deaths.
3. During March, seven patients with chronic encephalitis lethargica were given Rosenow serum subcutaneously. It was planned to treat another seven with the same dose by nasal spray. Five others have received 500 milliamperes current by diathermy for 20 minutes to the brain, and have reported subjective improvement.
4. Experiments on use of autocondensation current in multiple sclerosis.

"From Perry Point:
1. One hundred paretics have been given malaria treatment.
2. Two paretics were treated with sulfosin. The reaction was so severe that the study was stopped.
3. Twenty–nine epileptics were treated with a meat-free diet. They had no weight loss, and appear to be well. The severity but not the number of their convulsions has improved.
4. In accordance with instructions from the Research Subdivision, Central Office, the results of liver feeding in patients with neurological symptoms are being studied."[208]

Later in 1930, in a more complete report of research activities in field hospitals coordinated by his office, Dr. Matz listed four projects "recently assigned" to field hospitals and 19 projects from field hospitals for which final reports had been received (Table 2.8).[209]

Table 2.7. Research problems at Veterans Administration hospitals (*Medical Bulletin*, 1930).

Recently assigned
1. The use of the Gerson-Sauerbruch regimen in the treatment of pulmonary as well as surgical tuberculosis.
2. A study of 1001 autopsy protocols for the purpose of correlating clinical and anatomic findings.
3. The application of the Shaw-MacKensie test for malignancy, for the purpose of ascertaining whether or not this precipitation test will yield information in the diagnosis of malignant disease.
4. Therapeutic use of liver in the degenerative diseases of the spinal cord.

Recently completed
1. The use of typhoid vaccine in the treatment of general paresis of the insane.
2. Study of 100 cases of dementia praecox and manic-depressive psychosis.
3. Two modifications of the Benedict quantitative determination of dextrose in the urine.
4. Standardization of cholesterinized alcoholic beef heart antigen for use in complement fixation procedures.
5. Evaluation of results obtained by the use of liver, liver extract, and insulin in the reduction of blood sugar in diabetes mellitus.
6. Comparison of results with Meinicke and Kline tests.
7. Improved method of staining tubercle bacilli in tissue cut by frozen section method.
8. A study of the Gregerson test for the detection of occult blood.
9. The ketogenic diet in the treatment of epilepsy.
10. A resume of 250 electrocardiographs.
11. The use of lipiodol in the treatment of bronchiectesis.
12. The use of sodium ricinoleate in the treatment of intestinal tuberculosis.
13. A study of intestinal tuberculosis.
14. Pernicious anemia in the Negro.
15. Liver feeding in organic neurological conditions.
16. Rapid precipitation test for syphilis.
17. The 'Zoning' phenomenon in complement fixation with cholesterinized alcohol beef heart extract.
18. Studies in venous pressure - its clinical application.
19. Buffered diluent as preservative for diphtheria toxin for the Schick test.

A new approach in the 1930s: Centrally funded research laboratories

When the Veterans Administration was formed in 1930, the Medical Department found itself two layers down in the bureaucracy. Despite this, the Research Subdivision remained active through the mid-1930s. In 1931, Mr. George E. Ijams, Director of the Veterans' Bureau (now part of the Department of Veterans Affairs) said in his address to the Medical Council:

> "I am very glad to advise you gentlemen of a little meeting held here in Washington just a few weeks ago, and attended by some members of your body who were good enough to come over here and assist us. At that meeting was brought up a matter that has been close to my heart for some time, the matter of research. I do not claim any authorship for this, as this was sold to me many years ago by a former medical director. He impressed upon me the fact that we have a vast reservoir of material that we were not using for the advancement of medical science. Dr. Griffith and I talked this over and we decided to do what we could towards securing funds for the employment of men who were qualified to do this work. We wanted these men to do research work only, and not be called upon every five minutes to make a physical examination or to consider Mary Jones's efficiency report, etc. Following the conference with members of this council, the recommendation was made to General Hines that this work be started in the bureau. We appreciated the fact that we could not hope to secure a great deal of money for this purpose. We felt it would be much better to start in a modest sort of way and sell the idea by producing results. I am quite confident that if we can show results in the start of this work we will then have no difficulty in the future in securing whatever funds may be needed to carry on.
>
> "General Hines has approved this idea in principle, and I think that funds will be made available during the next fiscal year, beginning July 1, to enable us to start this most important work."[210]

Figure 2.5. Col. George E. Ijams

Despite this promising start, the outcome of that decision seems to have been limited to the establishment of a single funded cancer research laboratory in 1933, at the Hines VA Hospital in Chicago. This laboratory was primarily responsible for research, but it was also closely integrated with the patient care program of the hospital.

In 1935, the VA's Medical Director, Dr. Charles Griffith, called a second meeting about research. The meeting also involved members of the Medical Council, Drs. Barker, Adams, Thomas F.

Barrett, Cohn, William F. Lorenz and White, and other experts.[211] Apparently feeling that their efforts at the Hines hospital took care of the cancer problem, the Medical Department decided that the VA's major research needs were in neuropsychiatry and cardiac disease and had set aside $15,000 in their annual budget for each of these new initiatives, the same sum already being allotted to the Hines laboratory. Some of the conferees felt that this amount of money was so ridiculously small that there was no point in even planning a program. Dr. Lorenz told the group that New York State was spending $50,000 on research in neuropsychiatry alone. After considerable general discussion, the conferees split into two groups, one for neuropsychiatry and one for cardiology. Each group recommended that a laboratory in its field be established, and that the available monies be used for hiring two professional leaders. The review of this meeting published in the *Medical Bulletin* placed the cardiovascular research unit at the Washington, D.C., VA Hospital and the neuropsychiatric research unit at the North Chicago VA facility.[212] However, on the same page in the *Medical Bulletin* is the announcement of a new neuropsychiatric research unit at the Northport, N.Y., VA facility.[213] It appears that the unit proposed for North Chicago was cancelled in favor of Northport; but the cardiovascular research unit at the Washington, D.C., hospital did indeed open, in late 1935.

The Tumor Research Unit at the Hines VA Hospital

In 1932, the Tumor Research Laboratory at the Hines VA Hospital, the first research laboratory to receive funds from VA Central Office specifically for research work, was established to collaborate with the Hines Cancer Treatment Center. This special cancer treatment unit, a referral center modeled after Memorial Hospital in New York, had been established at Hines in 1930 in association with the new Diagnostic Center there. Surgeons, radiologists and organ-systems specialists worked together. A Tumor Board met daily to examine and discuss patients. There was an active teaching program with local and national conferences and an arrangement for training visiting physicians. It had the latest cancer therapy equipment, most notably a gram of radium and all necessary machinery for preparation and implantation of radon beads into cancer patients.[214] The research laboratory complemented this effort.

Seward E. Owen, Ph.D., a biochemist, initially led the Hines Tumor Research Laboratory. His early work was directed to assays of "prolans." (The term "prolan" was used at that time to define the substances excreted in the urine that cause positive pregnancy tests in animals; the effect is that of chorionic gonadotropin.) These substances were interesting to the Hines Tumor Clinic researchers because they observed that prolans were increased in most malignant testicular tumors, particularly the less well-differentiated tumors. The term "teratoma testis" was used to include a spectrum of testicular tumors, including chorionepithelioma; embryonal adenocarcinoma, without and with lymphoid stroma; seminoma; and mixed or adult-type testicular cancer. Prolan concentration in the urine varied by type of teratoma testis, with the highest concentration seen in chorionepithelioma and the least in the adult type. Owen developed a quantitative bioassay for prolans,[215] first in the rabbit and then in the mouse, for which he reported an innovative, inexpensive metabolic cage.[216] Collaborating with Max Cutler, M.D., Chief of the Tumor Clinic, he did extensive clinical correlations of this method in patients with testicular tumors.[217, 218] The method was used for follow-up of treated patients who lived at a distance from the hospital; they sent in their urine specimens by mail and were recalled for further treatment only when the results suggested recurrence. The method was applied to diagnose and follow two cases of chorionepithelioma[219] and five cases of malignant

tumors in undescended testes.[220] In 1936, Owen reported results of prolan assays in 71 patients who were later proven to have "teratoma testis," compared with 29 in whom it was suspected who later proved to have other diagnoses. From this study, he defined the diagnostic level of urinary prolans. Follow-up studies showed reduction in prolans after surgery and radiation with increase on recurrence of the tumor. False positives were found in three patients who had received orchiectomy for other conditions.[221] Owen and Cutler studied patients with prostatic hypertrophy and prostate cancer, measuring prolans and estrogenic substances by mouse bioassay. They found no abnormalities in those patients.[222]

This method of bioassay was very laborious and used many animals. Owen searched for a more economical method. He studied bitterling fish, into whose water the assay substances were placed.[223] The male bitterling fish develops a typical mating coloration when sexually stimulated; the female develops an extension of the ovipostor. After the responses of the fish to urine from pregnant women had been confirmed, urine extracts from patients with testicular tumors were tested. Female fish responded only to extremely high concentrations. The male fish generally responded to the concentrations of clinical interest, but their response was too erratic to make fish a practical substitute for rabbits and mice in this bioassay. Owen also tested these fish for a testosterone bioassay but concluded that a better understanding of their color responses was needed before a practical test was possible.[224] He also developed a chemical assay for the prolans,[225] which correlated fairly well with the bioassay and which he concluded would be a useful "qualitative" tool.

Owen also searched for agents that might cause malignant growth. In a series of articles in the journal *Growth*, he explored the role of the sulphydryl amino acids cystine and cysteine on wound healing in mice[226] and on extracts of insect larvae,[227] and he studied the release of sulphydryl groups from protein substances when they were exposed to carcinogens.[228] He published review articles about carcinogenesis.[229, 230] Collaborating with H.A. Weiss, M.D., and L.H. Prince, M.D., he reported in *Science* and the *American Journal of Cancer* that various carcinogens stimulate regeneration and reproduction in the planarian, an aquatic worm that regenerates both head and tail segments when cut in half.[231, 232] He also studied radiation effects in a high-breast cancer strain of mice. Irradiation reduced the incidence of later spontaneous breast cancer compared with similarly bred control mice, but not to the low incidence seen in randomly bred mice. He speculated that the irradiation may have reduced ovarian function and estrogen secretion, but noted that even nonsterilizing doses of radiation had a protective effect.[233] Following up on the likelihood that estrogens increase susceptibility to breast cancer, he and G. R. Allaben, M.D. of the Tumor Clinic published a case report of a woman with breast cancer that they believed was caused by prolonged estrogen therapy.[234]

When Owen left to join the military in 1938, Dr. Cutler, though still a consultant, became nominal head of the Tumor Research Laboratory. In fact, the laboratory seems to have lain dormant. Robert Schrek, M.D., was recruited from the St. Cloud (Minn.) VA Hospital to Hines.

Figure 2.6. Robert Schrek, M.D.

Schrek was a pathologist who had done basic oncologic research at Vanderbilt University. [236-244] When his Vanderbilt fellowship ended, Schrek went to work as a pathologist at the Pondville Hospital in Wrentham, Mass. While there, he did clinical research studies on cutaneous carcinoma that eventually led to three publications.[245-247] He entered VA at St. Cloud and immediately began looking for an opportunity to do research. Though his transfer orders to Hines instructed him "to work in the Tumor Research Laboratory," Dr. Schrek arrived to find that he was needed full-time in clinical service, and he was not able to start working in the research laboratory until 1940 or 1941.[235]

Schrek's earliest publications from Hines presented statistical methodology.[248-250] These publications seem to have resulted from work done on his own, before the research laboratory reopened. He also wrote a descriptive and statistical review of the Hines Tumor Clinic's 1941 activities.[251] Early in his days at Hines, Schrek formed a club with members from all Chicago area medical schools interested in cancer. During the war, Dr. Schrek became a Major in the U.S. Army, but his assignment was to continue work in the Tumor Research Laboratory.[235]

At first, the laboratory consisted of Schrek and two technical people. They set up a method that he had devised while at Vanderbilt to distinguish viable white blood cells from dead cells using the fact that only dead cells take up eosin in solution.[243] They used this method to assess factors affecting leukocyte life span. These studies were very laborious, as cell counts were done by hand-counting cells in a hemacytometer. Schrek obtained reasonably pure preparations of lymphocytes from rabbit thymus and spleen, and of polymorphonuclear leukocytes from rabbit bone marrow and from peritoneal exudate after intraperitoneal injection of an albumin-lecithin mixture. In short-term (two- to four-hour) experiments, he found that lymphocytes are much more sensitive to the toxic effects of heat and of moccasin venom than are polymorphonuclear leukocytes.[252] He found that oxygen was not necessary for cell survival, and that polymorphonuclear leukocytes survived equally well with or without glucose in the medium. Glycolysis occurred under both aerobic and anaerobic conditions. The major factor affecting cell survival was the type of cell. In studies of human leukocytes, he found that those from patients with lymphatic and myelogenous leukemias had the same metabolic characteristics as normal leukocytes.[253] In other studies, he showed that leukocytes are quite resistant to osmotic challenge,[254] and that the response of other tissues varies.[255]

Schrek's most noteworthy studies from the pre-1946 period were of the effects of radiation on leukocytes. Using his in vitro leukocyte preparation and a statistical method he devised to estimate 50 percent and 10 percent survival times, he clearly demonstrated marked radiosensitivity of lymphocytes, with considerable radioresistance of the polymorphonuclear leukocytes. This was equally true of preparations from the rabbit, from normal human blood, and from the blood of patients with lymphocytic and myelogenous leukemia. The cytocidal effect of radiation on lymphocytes was seen only in the presence of oxygen. Schrek recalled that when the paper reporting these findings was in press in *Radiology*, one of the editors visited him and suggested that he contact Austen Brues of the metallurgy department at the University of Chicago (predecessor of Argonne National Laboratory). Schrek did not follow up on this suggestion, which he later realized would have resulted in his being reassigned to atomic bomb research in the Manhattan Project.[256]

Meanwhile, Schrek continued to study patients in the Hines Tumor Clinic and to develop new methods.[257] He published a summary of 1,943 admissions in *Cancer Research*, pointing out that relatively more patients from the South presented with cancers of the exposed skin and relatively fewer with cancers of the stomach and testis.[258] He reported on a series of 20 black patients with skin cancers.[259] Five of these occurred at the site of a previous injury. While the incidence of carcinomas in sun-exposed areas of the skin was dramatically decreased in blacks, the incidence in covered areas of the body was similar in blacks and whites. He also studied the racial distribution of other cancers, using data from Hines and also from a U.S. Public Health Service survey and from national mortality statistics. He reported that carcinoma of the male breast was much higher in blacks than in whites, while the incidence of breast cancer in black women was only slightly greater than in whites.[260] Cancer of the penis and scrotum was increased in blacks.[261]

In the early post-war period, in collaboration with clinicians of the Tumor Clinic, Schrek reviewed the smoking histories of patients with cancers of the lung, larynx and pharynx, compared with those of the total population of cancer patients at Hines. He concluded that: "There is strong circumstantial evidence that cigarette smoking was an etiological factor in cancer of the respiratory tract."[262] This paper was later cited in the Surgeon General's report on the dangers of cigarette smoking.[263]

Figure 2.7. Robert Schrek, M.D., 1952

In his later work, Schrek continued to develop new techniques, one of the most useful of which was a time-lapse photography method using an inverted phase microscope.[264] Using this method, he showed that the in vitro radiosensitivity of the lymphocytes of a patient with lymphocytic leukemia was predictive of the patient's prognosis. In 61 patients with radiosensitive lymphocytes, median

survival was 22 months, while it was only four months in the 19 patients with radioresistant lymphocytes. This was not due to a change with time in radiosensitivity, as the patients with radiosensitivity continued to have radiosensitive lymphocytes throughout their clinical course.[265] He also described and characterized the "hairy cell," a previously unrecognized form of malignant white blood cell, and the course of hairy cell leukemia.[266]

Schrek seems to be unique among the pre-WWII VA research investigators in that he made a smooth transition to the very different post-war VA. At the end of the war, the Tumor Research Laboratory at Hines was transferred to local administration. The Hines hospital, as a referral center, already had many consultants from nearby medical schools. The atmosphere in the Tumor Clinic was academic, so the introduction of a formal medical school affiliation made less difference than it might have otherwise. Schrek remained at the Hines VA Hospital, in charge of the Tumor Research Laboratory, until he retired in 1977. He continued to analyze data and publish long after his retirement. After the war, he became a member of the pathology department of the Schools of Medicine of Northwestern University and later Loyola University, as they became affiliated with Hines. He collaborated widely, presented at national and international meetings and published 144 papers.

The Neuropsychiatric Research Units at the Northport VA Hospital

The neuropsychiatric research laboratory recommended by the 1935 conference was located at the Northport VA Hospital on Long Island in New York. In fact, two officially designated Neuropsychiatric Research Units were based at Northport, with a three-year lapse between them and apparently little or no overlap in staff. The first of these units, called the "Neuro-Psychiatric Research Unit for the Study of the Influence of Heterophile Antigen in Nervous and Mental Disease," was established in October 1935, and closed in October 1938. The announcement of its opening was published in the *Medical Bulletin*:

> "Upon authority received from the Administrator, a research unit was established in October at Veterans' Administration Facility, Northport, Long Island, N.Y., of which Dr. E.W. Lazell of the staff was placed in charge. The purpose of this unit is to investigate the nature of heterophile antigens and their significance in the diagnosis and treatment of certain diseases, particularly epilepsy. The personnel of this unit consists of Dr. E.W. Lazell, physician in charge; James E. Stanley, laboratorian in bacteriology; Mabel M. Blomberg, assistant laboratorian in bacteriology; Margaret Hickey, research clerk."[213]

In 1919 and 1920, Edward W. Lazell, M.D., had been a psychotherapist working for William A. White, M.D. at St. Elizabeth's Hospital in Washington, D.C., where attempts were being made to treat psychotic patients by psychoanalytic methods. In 1930, he wrote about an innovative method of applying psychoanalytic concepts to group treatment of psychotic patients.[267] He developed a concept of the unity of the mind and the body,[268, 269] which led him to try to identify a physical cause for neuropsychiatric disease. In 1929, he and Linnaeus H. Prince, M.D. (a pathologist whose name appears on research papers from a variety of VA locations) reported a search for a transmissible substance in the serum of patients with dementia praecox (schizophrenia).[270] This study was done while both Lazell and Prince had full-time clinical duties, but Prince, as a pathologist, had a laboratory at his disposal. They exposed bullfrog tadpoles to serum from normal and schizophrenic subjects and found that a 1:1000 dilution of normal serum was compatible with normal development

of the tadpoles. On the other hand, a 1:1000 dilution of serum of schizophrenic subjects uniformly killed the tadpoles within three days. They seem not to have pursued this fascinating finding, but Lazell quoted it in later work as seminal in his studies:

> "While trying to explain the phenomena shown in the pollywog experiment, our attention was casually directed to the existence of heterophile antigen. In this manner the toxic or lethal factor in the blood of epileptics and heterophile antigen became associated in our minds."[271]

Lazell then undertook a study of the general field of immunology, searching for an immune cause for neuropsychiatric disease. In 1932, he published a general review[272] focusing on the Forssman heterophile antibody, a type of antibody which has an affinity for the receptors of a species other than those in response to which it developed. Extrapolating from the observations that heterophile antibodies can be induced by feeding products from certain animals and could lead to allergic reactions, Lazell speculated that such a reaction might also cause such conditions as epilepsy and dementia praecox.

In the spring of 1935, Lazell studied a group of 14 Veterans, all committed as insane to Northport, who also were epileptic. He found that certain patients had convulsions after eating certain foods. By injecting rabbits with the suspect foods, he found that they developed a heterophile antibody, thus identifying the foods as heterophile antigens. He confirmed the food allergies by scratch and intracutaneous skin tests. Sera from 29 epileptic patients at a different hospital confirmed the presence of the heterophile antibody in those with idiopathic epilepsy, but not in those whose convulsions were due to syphilis or encephalitis. He concluded that the patients with idiopathic epilepsy and dementia praecox were sensitized to heterophile antigen, that these diseases are allergic in nature, and that the pathology followed ingestion of excessive amounts of heterophile antigen-containing foods.

Lazell presented these findings to the American Psychiatric Society on May 13, 1935.[273] From October 1935 to the end of 1936, the laboratory pursued this lead. On a research ward, the researchers intensively studied 36 patients with idiopathic epilepsy, four of whom also had dementia praecox. Finding that skin tests were unreliable and also sometimes triggered convulsions, they sought better ways to identify the allergens responsible for a patient's problem. They made extensive use of an observed leukopenic response to suspect foods. They tried elimination diets to prevent convulsions but concluded that so many foods had to be eliminated that such diets were impractical—the patients would starve. They concluded, "The greatest hope is offered by the search for a general desensitizer."[274]

One interesting finding from this research was the "epileptic cycle." Lazell and his colleagues observed that, after a seizure, the evidence of allergy (response to allergens in skin tests, circulating precipitins and leukocyte reduction) was reduced. It was a logical association, given the assumption that "there is a close connection between dementia praecox and idiopathic epilepsy," to hypothesize that induction of seizures might alleviate the symptoms of dementia praecox. This hypothesis directed their attention to insulin shock therapy, which was just coming into use in the United States.[274]

In early 1937, Dr. Lazell attended a training course at the Harlem Valley State Hospital in New York State on the treatment of schizophrenia with insulin coma. The course was directed by Manfred Sokol of Vienna, Austria, the originator of this treatment.[275] On his return to Northport, Lazell began to treat patients with insulin. Soon, Northport was set up as a training site, and between March 1937 and August 1938, 17 physicians from other VA hospitals were trained in this technique. As Lazell stated: "The work entailed by this training fell to the research personnel; and the laboratory studies necessary for the treatment and for these courses were done by them."[274]

The patients referred for insulin therapy were studied by the same methods used with epileptic patients. Lazell found that skin sensitization in dementia praecox patients was less marked in general and directed to different substances than was the case with patients with epilepsy. On the other hand, the leukopenic response to ingestion of certain foods was as marked in dementia praecox as in epilepsy, though the more frequent food allergens were different. Patients with dementia praecox and with epilepsy showed similar heterophile antibodies.

Following up on their observation that dementia praecox patients seemed to improve when seizures occurred during their insulin treatments, Lazell and his colleagues began adding metrazol to the treatment regimen. The logic of the combined treatment seems to have been that metrazol was more effective than insulin alone in inducing seizures, but that patients already in insulin coma developed seizures after a much smaller dose of metrazol than was otherwise needed.

Lazell and his colleagues attempted to desensitize patients with epilepsy and dementia praecox against the heterophile antigen. One substance they found promising was intravenous sodium oleate. While studies of this substance had not been completed when the laboratory was closed,[274] Lazell's team did demonstrate that sodium oleate, when applied directly to tissues, counteracted the effects of allergic dermatitis and hay fever.[276] In the report of this treatment, Lazell commented that,

> "One of the author's sons, overhearing the discussion about sodium oleate as a cure for ivy poisoning, went into the woods and deliberately squeezed a mass of poison ivy in both hands and rubbed it on his face, arms and legs. When seen the next day, they were very red; but the immediate use of sodium oleate as a wet dressing justified this youngster's confidence."

In 1937, Lazell was joined at Northport by Emanuel Messinger, M.D., a psychiatrist[277] who had been at the St. Cloud (Minn.) VA Hospital and earlier at the VA in Lyons (N.J.). Despite being a psychiatrist, Messinger had published about cardiac function.[278] After moving to Northport, he began studying the cardiovascular changes associated with insulin shock treatment, which he reported in the *Annals of Internal Medicine.* He showed that, during insulin coma, the heart, aorta and pulmonary artery dilate markedly.[279] Collaborating with Nathan Moros, M.D., Messinger published an article on the cardiovascular effects of metrazol, written in early 1938 and published in 1940, that reported transient tachycardia and cardiac arrhythmias.[280]

This laboratory was officially closed in October 1938, a few months after Dr. Matz died. Lazell published his final report of the laboratory's work in 1940.[274] All told, some 45 reports were issued from this laboratory.

A new Neuropsychiatric Research Unit of a different character was set up at Northport in 1941. James A. Huddleston, M.D., was the director and William J. Turner, M.D., was in charge of laboratory activities. Other staff included a biochemist, a statistician, a laboratorian, a laboratory assistant and a secretary-stenographer. This new laboratory was under the immediate supervision of Hugo Mella, M.D., the Central Office Research Chief. It had multiple responsibilities: In addition to "conduct of clinical and laboratory research in neuropsychiatric disorders," it was responsible for "standardization of diagnostic and treatment methods in neuropsychiatry" and for "teaching modern concepts and methods in neurology, psychiatry and neuropathology to physicians of the VA detailed for courses of instruction."[281]

An early product of this new laboratory was a review by its statistician, Charles S. Roberts, M.D., of the long-term results of the pharmacologic (insulin and metrazol) shock therapies that Drs. Lazell and Messinger and their trainees conducted in 1937 and 1938. They matched cases with untreated hospitalized control patients of like time of admission, age, sex (all males), race, diagnosis and prior length of psychiatric illness. They followed 74 treated-control pairs for at least two years after the shock therapy, 60 pairs for at least three years. Using a standardized scale of clinical status, they rated the pairs of patients at 30 to 90 days after completion of the treated patient's series of treatments and after one year, two years and three years. Two of the treated patients died during the treatment. Twenty-one (28 percent) of the treated patients and 10 (14 percent) of the controls showed some improvement at some time. No treated patients, and only one control, were considered "cured" at follow-up. At evaluation 30 to 90 days after completion of the treatment series, 21 percent of the treated patients were "improved" or "much improved," while only 8 percent of the controls were so classified. This difference gradually eroded with longer follow-up: Early in the second year, improvement was 19 percent and 7 percent, respectively; in the third year, 8 percent and 8 percent; and in the fourth year, also 8 percent and 8 percent. Roberts concluded that the main effect of pharmacologic shock therapy "appears to be that of facilitating improvement of a transient nature."[282]

A series of papers reporting systematic clinical observations of important neuropsychiatric conditions emerged from the staff of this new laboratory: "The alcoholic personality: a statistical study"; [283] "Some dynamic aspects of alcoholic psychoses";[284] "Factors in the development of general paralysis";[285] and "Note on psychoses and psychoneuroses with malaria."[286] The researchers also reported on their early work on electroencephalography.[287, 288]

This group also carried out biochemical tests. They studied trioses in the blood and devised an improved method for measuring blood hydroxyacetone, publishing their findings in the *Journal of Biological Chemistry*.[289] Results of clinical application of this method were negative. Blood glucose and diastase were studied in a group of depressed patients with manic-depressive psychosis, comparing results with a standardized-scaled psychiatric examination. They found that "voice loudness," "speech rate" and "facial expression of sadness" were all positively correlated with glucose levels, while "voice loudness" correlated negatively and "apathy" positively with diastase levels. The report of this study, of which Roberts was first author, reflects a sophisticated approach to probability and statistics.[290]

This group's publications about electric shock therapy, which appeared in 1945 and 1946, included articles about prediction of outcome,[291] method[292] and complications.[293-295]

No post-1946 record of this laboratory has been found.

The Cardiovascular Research Unit at the Washington, D.C., VA Hospital

The third pre-war official VA research laboratory was the Cardiovascular Research Unit at the Washington, D.C., VA Hospital. Like the Northport laboratory, it was established shortly after the 1935 Central Office conference about research.[211] The earliest of its published reports is a 1937 review in *Annals of Internal Medicine* by John Reisinger, M.D., the unit's Chief, presenting observations about the hospital's hypertensive patients from October 1, 1935, to April 1, 1936.[296]

In 1938, statistician Blanche Wilcox, Ph.D., and Reisinger collaborated on a study of the prediction of heart weight (confirmed at autopsy) from the x-ray.[297] Dr. Wilcox remained with the unit until it closed in 1949.

Publications from this laboratory were primarily statistical analyses and reports of advances in clinical cardiology and systematic observation of cardiology patients. The statistical analyses followed incidence of heart disease at the Washington VA hospital and also presented comparative data from Midwestern and Western VA hospitals.[298-300]

Reisinger wrote on the uses of the Masters exercise test[301] and the cold-pressor test.[302] An article in the *Archives of Internal Medicine* reported four cases of dissecting aneurysm proved at autopsy, including two observed for three and 14 months before death.[303, 304]

Reisinger also reported a case of primary tumor of the inferior vena cava.[305] He and Basil Blumenthal, M.D., who was probably a consultant to the Unit rather than a staff member, published their observations about the pain of coronary artery disease and myocardial infarction.[306-309]

In 1943, Reisinger published on "neurocirculatory asthenia," with data from a review of 50 World War I Veterans with this diagnosis. Neurocirculatory asthenia was the term used for a condition known in the Civil War as "irritable heart of soldiers" and by the British in World War I as "soldier's heart"[310] or "effort syndrome." Patients "manifested physical unfitness which could not be accounted for by auscultation of the heart or by any other methods of examination." He recorded good experience of others with gradually increasing physical training for these patients and recommended that such a program be established for the large number of such patients expected to emerge from service in World War II.[311]

Milton Mazer, M.D., joined the Unit around 1941 and remained for a year or two after Reisinger joined the Navy in 1942. He and Reisinger published a review of thiocyanate treatment of hypertension, with a report of nine cases.[312] Mazer published technical papers on the heart X-ray and electrocardiogram,[313-316] and he wrote an article on "Palindromic rheumatism."[317] He and Albert Kistin, M.D., who was active in the Unit after the war, wrote a pair of articles for the *Medical Bulletin* on "Current practice in cardiovascular diseases."[318, 319]

Aaron H. Traum, M.D., was the Chief of the Unit at the end of World War II. He and Blanche Wilcox reviewed extensive records from the experience of the Unit. They also reviewed thousands of records of service members being discharged from the military. They published in the *New England Journal of Medicine* a survey of 19,870 cases of cardiovascular disease from the pension rolls of World War II Veterans.[320] Of these cases, 44 percent had valvular or rheumatic heart disease; 15 percent were hypertensive; 9 percent were arteriosclerotic; 13 percent had peripheral vascular disease; 6 percent had neurocirculatory asthenia; and 13 percent had other conditions. Seeking better ways to screen out persons with heart disease before induction into the military, Traum and statistician Wilcox performed a complete record review of 150 of these Veterans, whose heart conditions had the same distribution as found in the larger series. They reviewed the Selective Service questionnaires and examination records, as well as all subsequent records, and found that in many cases the Veteran had known of his condition before induction and that some of them had mentioned it on the questionnaire. In a number of cases ultimately discharged for hypertension, no blood pressure had been recorded at induction.[321]

Traum reviewed the 10,500 patients who had received electrocardiograms at the Washington, D.C., VA Hospital between 1936 and 1944 and found 259 with right axis deviation. From these, he identified 26 patients with definite diagnoses of arteriosclerotic (22 patients) or hypertensive (four patients) heart disease. Comparing them with the much larger numbers of patients without right axis deviation, he found that only 9 percent of the arteriosclerotics with right axis deviation had died, compared with 20 percent of 573 other patients with arteriosclerosis. On the other hand, three of the four hypertensives had died compared with a 32 percent death rate among 737 other hypertensives, suggesting that right axis deviation might be a poor prognostic sign in hypertensives but a good one in arteriosclerotic heart disease.[322] He also published a case history uncovered in his record review of a 47-year-old World War I Veteran with Lutembacher's Syndrome, a congenital condition which usually caused death before age 40. This condition had not been detected during military service or, indeed, until the patient was about 40 years old.[323]

In terms of its wide recognition and lasting significance, the most important product of the Washington VA Hospital Cardiovascular Research Unit was a 1948 study of coronary artery disease in men under age 40, in which Traum and Wilcox collaborated with members of the Armed Forces Institute of Pathology.[324] This study reviewed 450 Army men under age 40 who had died of coronary disease and were studied at autopsy, as well as 416 Army men under age 40 who had survived well-documented episodes of myocardial infarction. From an extensive review of the literature, they found previous reports of a total of 744 deaths from coronary artery disease in persons under age 40, with a 27:1 male: female ratio. In their study, they collected demographic information and medical histories from interviews of survivors and questionnaires sent to relatives of those who had died. They used a variety of control groups: amputees, those with gunshot wounds and, where appropriate, the Army as a whole. They found increasing incidence of coronary disease with age within the age groups studied. Compared with controls, the men with coronary artery disease were more likely to be hypertensive and to have a family history of heart conditions. The authors could not demonstrate a relationship with smoking, alcohol intake or obesity. Incidence in blacks was about two-thirds that in whites. The clinical and pathological features of the heart attacks and subsequent course in these young men were similar to those observed in coronary artery disease in older persons.

In September 1948, Milton Landowne, M.D., arrived at the Washington, D.C., VA Cardiovascular Research Unit as its new Chief. He had trained extensively in cardiology and had joined the faculty of the University of Chicago. During the War, he had studied the pneumoconioses while assigned to the Public Health Service.

When he arrived, Dr. Albert Kistin and Blanche Wilcox, the statistician, were on the staff of the Unit. The Unit's physical plant, Landowne recalled, was quite large, occupying most of a wing of the hospital. The Cardiovascular Research Unit performed the electrocardiograms and angiograms for the hospital. It had a chemistry laboratory and facilities for housing and studying dogs. Office space was plentiful. Support staff included two electrocardiograph technicians, an animal technician and secretaries, and recruitment of a chemist was authorized.

The research under way was centered on angiography and electrocardiography. Kistin was very much interested in angiography and had invented an improved cassette changer.[325] George Robb, M.D., a cardiologist from Johns Hopkins who was interested in angiography, had influenced the VA to do advanced angiography in its Cardiovascular Research Unit, and he had arranged for a prototype fluorescent image amplifier from General Electric to be placed there. This had not yet arrived when the Unit was closed in late 1949, but meanwhile, Robb collaborated with Kistin in electrocardiology. They published an analysis of the normal esophageal and gastric electrocardiogram [326] and a case report of the effects of Wolff-Parkinson-White Syndrome on the electrocardiogram in myocardial infarction.[327]

Kistin published on the anatomy of the bundle of His[328] and on optimal placement of electrocardiography electrodes.[329] With other clinicians, he published on two cases of paralysis of the recurrent laryngeal nerve in rheumatic heart disease[330] and a case of an anomalous pulmonary vein proven by angiography.[331]

After Landowne arrived, he and Kistin worked together trying to understand the cause of premature ventricular contraction (PVC) of the heart. They recorded esophageal electrocardiograms on 33 patients whose traditional electrocardiogram showed frequent PVCs. Fifteen of them, including six with normal hearts, showed evidence of retrograde conduction from the ventricle to the auricle.[332, 333] The researchers also reported on the diagnostic signs of ventricular aneurysm, based on eight cases they had demonstrated angiographically.[334] They did a comparative study of electrocardiography machines with Solomon Gilford, B.S.E.E., an engineer at the National Bureau of Standards.

In July 1949, just 10 months after he arrived, Landowne received sudden word that the Unit was to be closed. He and Dr. Kistin were offered the opportunity to continue their research at a different VA hospital, but both preferred to leave the organization. Kistin went into private practice and later worked with miners in West Virginia suffering from pneumoconioses. Landowne joined the NIH Aging Study Unit (under Nathan Shock, Ph.D.) in Baltimore. The Cardiovascular Research Unit officially closed in November 1949. [335]

Decline in the research program

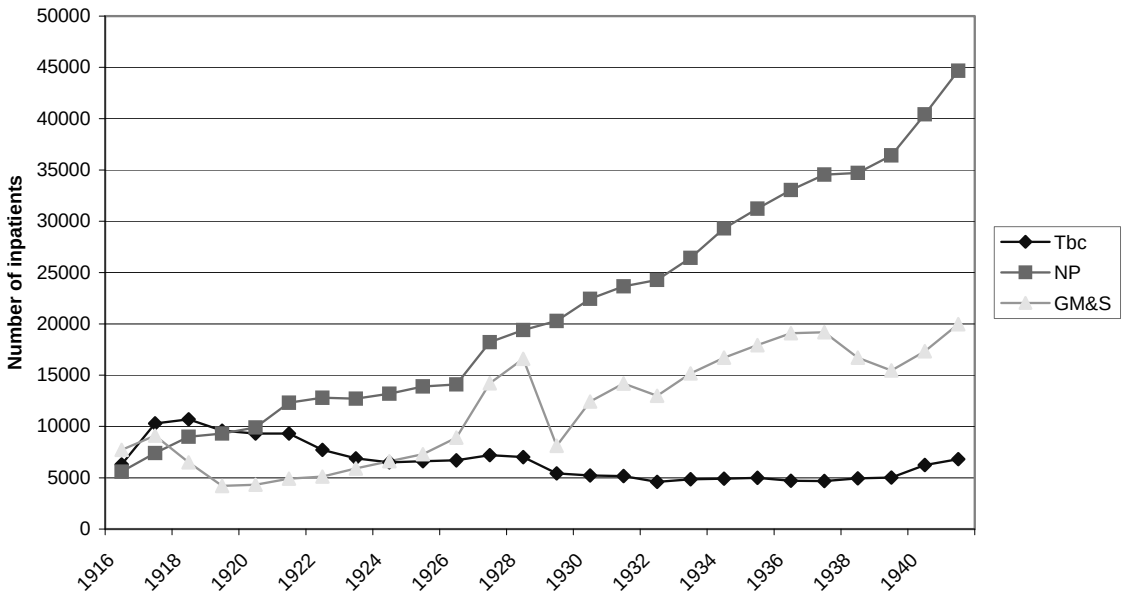
There seems to be little question that the enthusiasm for excellence in the veterans' hospital system of the 1920s had waned by the middle of the 1930s. This happened despite the fact that medical

progress was occurring in the VA, as reflected in the *Medical Bulletin*. Much of this decline can be attributed to aging: of the agency leadership, the patients being served, and the physicians serving them.

General Hines continued as Administrator of the Veterans Administration until after World War II. The tight controls he had established in 1923, when he came in to reform a corrupt and wasteful agency, were now stifling.. Dr. Griffith, his Medical Director from 1931 through the war, is described as an amiable person who subordinated himself to Hines's direction.

The patient population changed as the World War I Veteran aged (Figure 2.8). Many of the tuberculous patients who filled the hospitals in the early 1920s had either died or improved. The acute illnesses and injuries of the young had mostly resolved or no longer required hospital care. Now, more VA patients suffered from the diseases of middle age, especially heart disease and cancer. The syphilitics left in the hospitals were the hopeless cases with tertiary disease, especially neurosyphilis. The population of patients with psychoses continued to increase, as there was no effective way to control these dread diseases even though the patients generally lived a near-normal life span. By 1941, nearly 60 percent of VA patients suffered from neuropsychiatric diseases. These were patients who did not appeal to many physicians, as the rewards of caring for them were small.

Figure 2.8 Patient care load in the VA before the end of WWII



At the same time, the mechanics of recruiting and retaining quality physicians for the veterans' hospitals under the Civil Service system was a constant problem. The attempts to set up a medical corps for the VA had been unsuccessful, and the energy behind such attempts waned over time. Veteran preference under Civil Service laws generally meant that only physicians who were World War I Veterans were hired,[126] and they, too, were aging.

Final meeting of the Medical Council

After 1931, the Medical Council did not meet for eight years, a constraint attributed to tightened federal spending during and after the Depression. When they were called together once more in 1939, the members were not pleased with what had been happening in their absence. They noted that the character of the Diagnostic Clinics had changed. These Centers no longer confined their activities to diagnosis. Now their efforts were diluted with treatment activities.[336]

The Research Group was particularly unhappy with the way things were going, as indicated by a report read by Dr. Louis Dublin:

> "Your Research Committee has, from the very beginning of the Council, repeatedly stressed the importance of research as an essential activity in the Medical Service of the Veterans Administration. It has been our opinion that a research unit would pay for itself many times over in the better administration of the Medical Service, as well as in an advancement of medical knowledge. Yet, in spite of such recommendations, often reiterated, the Administration has not developed such a research organization….
>
> "To be sure, Dr. Matz did organize a very simple but effective unit of statistical investigation. Some research activities have also been conducted in individual hospitals, with commendable results. Here and there, individual physicians have taken advantage of their opportunity to record their experiences; but all these efforts, in our judgment, do not constitute an adequate approach to the research problem of the Veterans Administration."
>
> "... Any organization which is concerned with the hospitalization of tens of thousands of patients annually, and which spends many millions of dollars, must in the very nature of the case, organize itself for effective self-criticism, and for the analysis and solution of problems which arise out of its varied operations. To do that, the first consideration is a leader, who by training and aptitude would be competent to carry on the work in a manner equal to the opportunity. At no time in the past has there been available this essential of a research organization. We believe that little progress will be made in this direction until this first step is taken. With such a step there would be a possibility of a development commensurate with the richness of the material which is available."
>
> "... Finally, the Research Committee believes that the development of a research organization, with the Medical Service, should not be carried on without consultation with it. It is impossible to advise the Administration with any effectiveness if appointments of heads of divisions are made without consultation, and the Research Committee finds itself confronted with accomplished facts, which in its judgment stand in the way of a development such as it has in mind."

They presented a plan for a research organization with a Central Office staff that would work with all major divisions of the Medical Service, addressing the most pressing problems of each. Research "would not be limited to statistical investigations alone. The statistical method lends itself, of course, to the conduct of research in administration, therapeutics, the natural history of disease and analysis of disease processes. All of these fields should be the subject of investigation."[337]

The group also recommended establishing separate research units in some of the larger hospitals, citing the Tumor Research Unit at Hines, attached to the Tumor Clinic at Hines, and the Cardiovascular Research Unit, attached to the cardiac clinic at the Washington, D.C. hospital as a beginning in this direction.

The Council as a whole showed their displeasure that their advice was not being sought as much as in the past. They urged that they be called together annually.[338] As Dr. Barker commented, "I think this meeting has shown that the Councillors have a deep interest in the welfare of the Veterans Administration and that they have many suggestions that will be helpful."[339]

Although there were occasional later meetings of the Executive Committee and individual members were called on to inspect hospitals, there were no further meetings of the full Medical Council after this October 1939 meeting. The advice about research and other activities proffered in October 1939, unlike the advice of the 1924 Medical Council, went unheeded.

In 1944, Hines appointed a new advisory group, with George M. Piersol, M.D. and Dr. Roy Adams as Chairman and Secretary and including William F. Lorenz and Malcolm MacEachern, M.D. Joining these members of the old Medical Council were 12 other physicians, each representing a medical specialty. This Special Medical Advisory Group was short-lived. It met three times during early 1945, appears to have effected no changes, and disbanded when Hines left in August 1945.[340] It was replaced by a new Special Medical Advisory Group mandated in the 1946 law that established the Department of Medicine and Surgery (Chapter 3).

Wartime changes

No recorded changes in the VA research program occurred as a result of the concern of the Medical Council advice, and soon wartime stresses took their toll. During World War II, many of the younger VA physicians left for the military. Not until 1943 was the VA declared a national priority. In a move to preserve a coherent medical staff, Administrator Hines arranged for VA's remaining physicians to be commissioned military officers, with the same salaries, benefits and recognition as their colleagues in the camps and war fronts. But by this time, the physician ranks in the VA were so depleted that supervision of patient care became very difficult.

As Paul Magnuson, M.D., described in his autobiography, during his 1946 visit to the Palo Alto VA Hospital he found a facility in chaos::

> "I didn't expect much, but the place gave me a shock. They had five doctors there, taking care—question mark in a very large way—of one thousand patients. The outside of the facility was very nice, with well tended shrubs and flowerbeds, but what went on inside was just beyond description."[341]

His account contrasts sharply with the upbeat institution described by Dr. Ray Wilbur in 1924, when he wrote of the Palo Alto Veterans Hospital that "the whole aspect of the hospital is one of cheer and hopefulness as compared with the ordinary institution of the sort."[342]

There were, of course, exceptions. An occasional clinician still conducted research, as seen in the discussion in Chapter 3 of the work of Ludwig Gross,M.D. However, judging by the papers published in the *Medical Bulletin* during its last 10 years of publication, 1935 through 1944, original research seems to have almost disappeared in the hospitals except in the formal centralized research laboratories.

In November 1944, in response to an inquiry from Albert Q. Maisel, a reporter who later wrote a scathing article in *Reader's Digest*[343] about the VA, Ray Lyman Wilbur wrote:

> "... In my judgment the principal difficulty has been that the whole problem of medical service was gauged on too low a financial level and that priorities were given to Veterans throughout the whole organization sometimes regardless of their skills and training.
>
> "The Medical Council was desirous of developing research and putting in superior men in the hospitals to carry it on, so that the work of the hospitals would not become largely custodial but would provide a series of research studies on a gradually aging group with the ailments that come with the years. . . . If some diagnostic and research centers could be established under the complete control of some of the best medical men developed by the war I believe that it would be worth while financially and in every other way."[344]

Wilbur went on to urge salary increases for VA professional staff, pointing out that "in the Indian Health Service and in the Veterans Hospital service, generally speaking, the salaries paid and the conditions of service have not attracted the best trained and the best qualified doctors and nurses."

Wilbur sent a copy of this letter to General Hines, whose response did not acknowledge these problems. With regard to research, Hines wrote:

> "I know that you will be glad to know that there are three research units now being operated by the Veterans Administration. The unit at Hines, Illinois, conducts extensive research on tumors and enjoys an enviable reputation with research workers throughout the country interested in this field. The unit at Washington, D.C. is utilized for research covering the field of cardiology, while the more recently established unit at Northport, Long Island, devotes its time to research problems in the neuropsychiatric field.
>
> "The established research units are not only working on basic projects in medicine but are concentrating on problems concerned with disabled Veterans. The units are staffed by outstanding medical officers and superior auxiliary personnel who have been carefully selected for the specific type of work to which they are assigned. Each unit has made contributions to scientific literature. In addition, many medical officers throughout the Service are also working on research problems."[345]

Despite what Hines portrayed, there is very little evidence of research being done during the war in the VA hospitals, except in the research units.

By the time a new VA medical research effort started up in 1946, it was indeed a new beginning. Eventually, today's strongly academic VA research program grew in conjunction with the agency's

post-war collaboration with medical schools. However, this was a gradual and incomplete transition; some research continued in hospitals with weak affiliations or even without medical school affiliations. This post-World War II research retained some of the post-World War I tradition of clinical research on the health problems of Veterans, carried out by individual physicians looking for better ways to treat their patients.

References

1. Rothstein, W., American Medical Schools and the Practice of Medicine. New York and Oxford: Oxford University Press, 1987, 235-236.

2. Chargaff, E., "In praise of smallness - how can we return to small science?" Perspectives in Biology and Medicine, 1980. 23: 374.

3. Cohn, A.E., "Purposes in medical research. An introduction to the Journal of Clinical Investigation." J Clin Invest, 1924. 1: 1-11.

4. Gregg, A., The Furtherance of Medical Research. London: Oxford University Press, 1941, 1-14.

5. Shryock, R.H., American Medical Research, Past and Present. New York: The Commonwealth Fund, 1947, 101.

6. Furman, B., A Profile of the United States Public Health Service, 1798-1948. Washington, DC: US Department of Health, Education and Welfare, 1973

7. Gregg, The Furtherance of Medical Research. 1941, 33.

8. Shryock, American Medical Research. 1947, 136.

9. Marks, H.M., The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990. Cambridge, New York and Melbourne: Cambridge University Press, 1997, 30-31.

10. Harvey, A.M., Science at the Bedside. Clinical Research in American Medicine, 1905-1945. Baltimore and London: Johns Hopkins University Press, 1981

11. Kohler, R.E., From medical chemistry to biochemistry; the making of a biomedical discipline. Cambridge, London, New York, New Rochelle, Melbourne, Sydney: Cambridge University Press, 1982

12. Wilbur, R.L., "Address to the Medical Council." US Veterans' Bureau Medical Bulletin, 1926. 2: 5-6.

13. Matz, P., "Research work in the United States Veterans' Bureau." US Veterans' Bureau Medical Bulletin, 1926. 2: 188-192.

14. Thompson, W.O., "Studies in blood volume: I. The blood volume in myxedema, with a comparison of plasma volume changes in myxedema and cardiac edema." J Clin Invest, 1926. 2: 477-520.

15. Marks, The Progress of Experiment. 1997, 53-60.

16. Marks, *The Progress of Experiment*. 1997, 43.

17. "Minutes of the Fourth Conference of the Medical Council." October 22-24, 1925, 40.

18. "The Establishment of Diagnostic Centers." *United States Veterans' Bureau Medical Bulletin*, 1925. **1**: 58-59.

19. "Death of Dr. Kennon Dunham." *US Veterans Administration Medical Bulletin*, 1944. **21**: 120.

20. Black, B.W., "Address of Medical Director B.W. Black to the Medical Council." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 584-586.

21. "Establishment of a new Diagnostic Center." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 287.

22. Swackhamer, W.B., "Organization and procedure in United States Veterans' Diagnostic Center." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 947-950.

23. "American Legion urges more Diagnostic Centers." *The Live Oak (US Veterans' Hospital, Palo Alto, CA)*, Menlo Park, CA, November 18, 1929.

24. "Death of Dr. Charles A. Elliott." *US Veterans Administration Medical Bulletin*, 1939. **16**: 191.

25. "Palo Alto Center expansion to wait." *The Live Oak (US Veterans' Hospital, Palo Alto, CA)*, Menlo Park, CA, October 18, 1931.

26. "Opening of facility at San Francisco." *US Veterans Administration Medical Bulletin*, 1935. **11**: 274.

27. "Ten doctors and 11 nurses move to San Francisco facility." *The Live Oak (US Veterans' Hospital, Palo Alto, CA)*, Menlo Park, CA, October 3, 1934.

28. Beardsley, L.G., "Procedure of medical study in United States Veterans' Diagnostic Center, Washington, DC." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 901-905.

29. Crossman, E.O., "Preface - United States Veterans' Bureau Medical Bulletin (introduction)." *US Veterans' Bureau Medical Bulletin*, 1925. **1**: vi.

30. "Notes and discussion." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 734-735.

31. "Special articles received for the Bulletin from the hospitals." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 301-303.

32. "Notes and discussion." *United States Veterans' Bureau Medical Bulletin,* 1925. **1**: 63-64.

33. "Minutes of the Fourth Conference of the Medical Council with the Director and the Medical Director of the United States Veterans' Bureau." October 22-24, 1925. Washington, DC, 1925, 25-26.

34. "Minutes of the Fourth Conference of the Medical Council." 1925, 26-27.

35. Matz, P.B., "Laboratory studies in influenza at Camp Travis, Texas." *Am J Med Sci*, 1919. **158**: 723 - 730.

36. Matz, P.B., "Studies on the calcium content of blood of normal and tuberculous subjects." *Am Rev Tuberculosis,* 1925. **II**: 250 -274.

37. Griffith, C.M., "Dr. Philip B. Matz." *Ann Int Med*, 1938. **12**: 280-282.

38. Matz, P.B., "Statistical studies on cardiovascular diseases in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1926. **2**: 304-307.

39. Matz, P.B., "Statistical studies of the mortality of heart diseases in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1926. **2**: 399-401.

40. Matz, P.B., "Statistical studies on tuberculosis in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1926. **2**: 793-794, 977-978, 1087-1090.

41. Matz, P.B., "Statistical studies on degenerative diseases in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1926. **2**: 1182-1189.

42. Matz, P.B., "Statistical studies on degenerative diseases in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 72-77.

43. Matz, P.B., "Statistical studies on neuropsychiatric disabilities in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 156-160, 253-259.

44. Matz, P.B., "Statistical studies on compensation in the United States Veterans' Bureau." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 376-389.

45. Matz, P.B., "Hospital statistics for November, 1926." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 611-617.

46. Matz, P.B., "Analysis of United States Veterans' Bureau Hospital statistics for December, 1926." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 728-736.

47. Matz, P.B., "Analysis of United States Veterans' Bureau Hospital statistics for January, 1927." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 818-824.

48. Matz, P.B., "Analysis of United States Veterans' Bureau Hospital statistics for February, 1927." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 931-944.

49. Matz, P.B., "Analysis of United States Veterans' Bureau Hospital statistics for March, 1927." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 1051-1060.

50. Matz, P.B., "Malaria treatment of general paralysis of the insane." *US Veterans Bureau Medical Bulletin*, 1926. **2**: 712.

51. Matz, P.B., "The treatment of neurosyphilis by means of 'inoculation malaria'." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 42-46.

52. Matz, P.B., "Report on the treatment of 179 cases of neurosyphilis by means of 'inoculation malaria'." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 387-389.

53. Matz, P.B., "Histopathology of the brain in paresis following malaria treatment." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 619-621.

54. Matz, P.B., "The preparation for transmission through the mail of malarial blood suitable for the treatment of paresis." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 944.

55. Matz, P.B., "The treatment of neurosyphilis by 'inoculation malaria' in the United States Veterans Bureau." *J Nerv and Ment Dis*, 1928. **68**: 113 - 133.

56. Teitelbaum, A.D., "Preliminary Report of Fifteen Cases of Sodoku Treatment of General Paralysis." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 263-270.

57. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: examination of sputum." *US Veterans Bureau Medical Bulletin*, 1928. **4**: 46-55.

58. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: the spinal fluid." *US Veterans Bureau Medical Bulletin*, 1928. **4**: 149-158, 265-277, 365-383, 463-474.

59. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: examination of gastric contents." *US Veterans Bureau Medical Bulletin*, 1928. **4**: 551-561.

60. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: examination of feces (Clinical Bulletin #23)." *US Veterans Bureau Medical Bulletin*, 1928. **4**: 711-716, 802-810.

61. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: blood chemistry." *US Veterans Bureau Medical Bulletin*, 1928. **4**: 871-880, 958-971, 1050-1060.

62. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: blood chemistry - the dietetic management of various diseases." *US Veterans Bureau Medical Bulletin*, 1929. **5**: 61-67.

63. Matz, P.B., "Standardization of clinical laboratory work in hospitals and regional offices: examination of transudates and exudates." *US Veterans Bureau Medical Bulletin*, 1929. **5**: 136-141.

64. Matz, P.B., "Preliminary report of board of medical officers on residual effects of warfare gassing." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 681-683.

65. Gilchrist, H.L. and Matz, P.B., "The residual effects of warfare gases: the use of chlorine gas, with report of cases." *US Veterans Administration Medical Bulletin*, 1933. **9**: 229-270.

66. Gilchrist, H.L. and Matz, P.B., "The residual effects of warfare gases: the use of phosgene gas, with report of cases." *US Veterans Administration Medical Bulletin*, 1933. **10**: 1-36.

67. Gilchrist, H.L. and Matz, P.B., "The residual effects of warfare gases: the use of arsenical compounds, with report of cases." *US Veterans Administration Medical Bulletin*, 1933. **10**: 79-98.

68. Gilchrist, H.L. and Matz, P.B., "The residual effects of warfare gases: the use of mustard gas, with report of cases." *US Veterans Administration Medical Bulletin*, 1933. **9**: 339-390.

69. Matz, P.B., "Outcome of hospital treatment of ex-service patients with nervous and mental diseases in the U.S. Veterans Bureau." *Psy Quar*, 1929. **3**: 550 -568.

70. "Increase of 6,264 in Veterans' Hospitals." *JAMA*, 1935: 1348.

71. Adkins, R.E., *Medical Care of Veterans*. 1967, 161.

72. Crossman, E.O., "Address to the Medical Council." *United States Veterans' Bureau Medical Bulletin*, 1929. **5**: 569-570.

73. Weber, G.A. and Schmeckebier, L.F., *The Veterans' Administration: its history, activities and organization*. Washington: The Brookings Institution, 1934, 319.

74. Matz, P.B., "A study of intestinal tuberculosis among exservice men." *Am J Med Sci*, 1930. **179**: 532-546.

75. Matz, P.B., "Future incidence of nervous and mental disease among ex-service men." *Am J Psychiatry*, 1930. **9**: 1043-1060.

76. Matz, P.B., "The Gerson-Sauerbruch dietetic regimen in tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 27-32.

77. Matz, P.B., "Study of diabetes mellitus among ex-service men." *Military Surgeon*, 1931. **68**: 591-635.

78. Matz, P.B., "The treatment of diabetes mellitus." *US Veterans Administration Medical Bulletin*, 1932. **8**: 331-350.

79. Matz, P.H., "A study of diabetes mellitus among ex-service men." *JAMA*, 1936. **106**: 2214 - 2221.

80. Matz, P.H., "A study of diabetes mellitus among ex-service men." *Military Surgeon*, 1937. **80**: 122 - 131.

81. Matz, P.B., "A study of diabetes mellitus in ex-service men." *US Veterans Administration Medical Bulletin*, 1931. **7**: 533-549, 625-642.

82. Matz, P.B., "A study of cancer in ex-service men." *US Veterans Administration Medical Bulletin*, 1931. **7**: 1010-1031, 1128-1149.

83. Matz, P.B., "The coincidence of malignancy and tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 939-942.

84. Matz, P.B., "A study of manic depressive psychosis in ex-service men." *US Veterans Administration Medical Bulletin*, 1932. **8**: 1-19.

85. Matz, P.B., "Clinical and economic features of arthritis in ex-members of the military service." *N Eng J Med*, 1933. **209**: 639.

86. Matz, P.B., "Habit-forming drugs." *US Veterans Administration Medical Bulletin*, 1934. **11**: 198-209.

87. Matz, P.H., "Food poisoning--its cause and its control." *Mod Hosp*, 1935. **45**: 90 - 94.

88. Matz, P.B., "Food poisoning in hospitals and domiciliary institutions." *US Veterans Administration Medical Bulletin*, 1935. **11**: 159-165.

89. Matz, P.B., "Malignancy and tuberculosis." *Mil Surg*, 1935. **77**: 207.

90. Matz, P.H., "The end-results of the surgical treatment of pulmonary tuberculosis." *Am Rev Tuberc*, 1936. **33**: 533 - 548.

91. Matz, P., "The incidence of primary bronchiogenic carcinoma." *JAMA*, 1938. **111**: 2086-2092.

92. Matz, P.B., "The dispensary care of disabled ex-service men." *US Veterans Administration Medical Bulletin*, 1932. **8**: 186-194.

93. Matz, P.B., "A study of heart disease among veterans: I. Clinical classification of five hundred cases." *N Eng J Med*, 1935. **212**: 868 - 874.

94. Matz, P.H., "A study of heart disease among veterans: II. Analysis of a group of cases as to age at onset and duration of heart disability." *N Eng J Med*, 1935. **212**: 929-932.

95. Matz, P.H., "A study of heart disease among veterans: III. Hereditary and famillial factors in the causation of cardiovascular disease." *N Eng J Med*, 1935. **212**: 977-978.

96. Matz, P.H., "A study of heart disease among veterans: IV. An analysis of the more frequent types of anatomic heart disease." *N Eng J Med*, 1935. **212**: 1042-1048.

97. Matz, P.H., "A study of heart disease among veterans: V. Syphilitic heart disease." *N Eng J Med*, 1935. **212**: 1087 - 1089.

98. Matz, P.B., "Pathology of the lungs and other organs in silicosis." *Military Surgeon*, 1937. **81**: 88.

99. Matz, P., "Roentgenologic classification and diagnosis of silicosis." *Am J Roentgenol*, 1938. **40**: 848-858.

100. Matz, P.B., "A study of silicosis." *Am J Med Sci*, 1938. **196**: 548-559.

101. Matz, P.B., "Pathology of the lungs and other organs in silicosis." *Am J Clin Path*, 1938. **8**: 345-365.

102. "Dr. P.B. Matz, Research Unit Chief, expires: famed pathologist was on tour inspecting Veterans' Hospitals." *Unknown (provided by Oscar Schabb, nephew)*.

103. Letter from Anne Bambery to Mrs. Joseph Rudolph, Baltimore, MD (letter provided by Oscar Schabb), written at Washington, DC, November 1, 1938.

104. Letter from Horatio M. Pollack to Medical and Hospital Service, VACO, written at Albany, NY, 1938.

105. Letter from Arthur J. Vorwald to Medical and Hospital Service, VACO, written at Saranac Lake, NY, 1938.

106. Mella, H., "The circulation of phenol sulphothalein in the cerebrospinal fluid." *J Nerv Ment Dis*, 1922. **56**: 599-601.

107. Mella, H., "Thrombotic cortical amaurosis: report of a case of bilateral calcarine softening." *J Nerv Ment Dis*, 1922. **56**: 563-566.

108. Mella, H., "The cerebrospinal fluid in jaundice." *Arch Neur Psychiatr*, 1922. **8**: 329-330.

109. Mella, H., "Irradiation of the thymus in myasthenia gravis." *Med Clin N America*, 1923. **7**: 939-949.

110. Mella, H., "The diencephalic centers controlling associated locomotor movements." *Arch Neur Psychiatr*, 1923. **10**: 141-153.

111. Mella, H., "Neurosyphilis as an etiological factor in the Parkinsonian syndrome." *J Nerv Ment Dis*, 1924. **59**: 225-230.

112. Mella, H., "The experimental production of basal ganglion sympathectomy in Macacus Rhesus." *Arch Neur Psychiatr*, 1924. **11**: 405-417.

113. Mella, H., "Bulbocapnin: its use in the treatment of tremor and in experimental production of basal ganglion symptomatology." *Arch Neur Psychiatr*, 1926. **15**: 325-329.

114. Ebaugh, F.G. and Mella, H., "The use of Lipiodol in the localization of spinal lesions." *Am J Med Sci*, 1926. **172**: 117-123.

115. Mella, H., "Improving our contact with relatives of patients." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 801-802.

116. Mella, H., "Panniculitis." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 697-698.

117. Mella, H., "The use of subarachnoid lavage and ethylhydrocupreine in meningitis." *US Veterans' Bureau Medical Bulletin*, 1931. **7**: 77-78.

118. Mella, H., "Loss of associated locomotor movements in diencephalic lesions." *US Veterans Administration Medical Bulletin*, 1931. **7**: 762-763.

119. Mella, H. and O'Neill, R.T., "Ultraviolet irradiation in general paresis." *US Veterans Administration Medical Bulletin*, 1932. **9**: 29-32.

120. Mella, H. and O'Neill, R.T., "Intravenous administration of sodium amytal in acute psychotic episodes." *US Veterans Administration Medical Bulletin*, 1933. **9**: 271-275.

121. Mella, H. and Blomberg, M.M., "A study of the absorption spectra of cerebrospinal fluid in the visible part of the spectrum." *J Nerv Ment Dis*, 1936. **83**: 685-688.

122. Mella, H., "Treatment of 43 cases of lobar pneumonia." *US Veterans Administration Medical Bulletin*, 1937. **13**: 247-250.

123. Mella, H., "Senescence and rejuvenation." *US Veterans Administration Medical Bulletin*, 1938. **14**: 322-328.

124. Mella, H., "A study of results of the treatment of neurosyphilis." *US Veterans Administration Medical Bulletin*, 1939. **16**: 106-119.

125. Mella, H., "Report of 92 cases of pneumonia treated with sulfapyridine." *US Veterans Administration Medical Bulletin*, 1940. **16**: 197-209.

126. Interview with Abraham Gottlieb, M.D., December 18, 1991 at Palo Alto, CA. VAMC

127. *Directory of Medical Specialists holding certification by American Boards, Volume VI, published for the Advisory Board for Medical Specialties*. Chicago: A.N. Marquis Company, 1953, 1022.

128. Ziegler, E.E., "The specific effect of bile salts on pneumococci and on pneumococcus pneumonia." *Ach Int Med*, 1930. **46**: 644-656.

129. Ziegler, E.E., "The effects on pneumococci of sodium dehydrocholate, a bile salt derivative III." *J Lab Clin Med*, 1931. **17**: 317-324.

130. Ziegler, E.E., "The effects on pneumococci of sodium dehydrocholate, a bile salt derivative." *US Veterans Administration Medical Bulletin*, 1932. **8**: 105-112.

131. Ziegler, E.E., "Pneumocholin; a new biochemical antigen." *US Veterans Administration Medical Bulletin*, 1933. **9**: 276-286.

132. Ziegler, E.E., "Some properties of pneumocholin, a biochemical antigen." *J Lab Clin Med*, 1933. **18**: 695-704.

133. Ziegler, E.E., "A new measurement of oxygen absorbing power." *Med Ann District of Columbia*, 1933. **2**: 225-230.

134. Ziegler, E.E., "A new measurement of oxygen absorbing power (preliminary report)." *J Aviation Medicine*, 1933. **4**: 119-129.

135. Stein, J.J., "The early diagnosis and treatment of cancer." *US Veterans Administration Medical Bulletin*, 1936. **12**: 412-421.

136. Stein, J.J. and Hantsch, F.K., "Adenocarcinoma of the rectum with unusual sites of metastases." *JAMA*, 1937. **108**: 1776-1779.

137. Stein, J.J., "Tumors of the small intestine: a review of the literature and report of eight additional cases." *Am J Digestive Diseases and Nutrition*, 1938. **4**: 517-522.

138. Stein, J.J., "Metastases to bone from carcinoma of the gastro-intestinal tract." *Radiology*, 1940. **35**: 486-488.

139. Stein, J.J., "The clinical and pathological features of tumors occurring in the region of the apex of the lung." *Texas State J Med*, 1937. **33**: 293-299.

140. Stein, J.J., "Apical lung tumors: further observations with report of seven additional cases." *JAMA*, 1938. **111**: 1612-1617.

141. Stein, J.J. and Joslin, H.L., "Carcinoma of the bronchus: a clinical and pathological study of 164 cases." *Surg Gyn and Obst*, 1938. **66**: 902-911.

142. Stein, J.J., "Bone metastases from primary carcinoma of the lung. Report of an unusual case." *J Bone and Joint Surg*, 1939. **21**: 992-996.

143. Stein, J.J., "Carcinoma of the lung: a clinical study." *US Naval Med Bull*, 1940. **38**: 329-334.

144. Stein, J.J., "Tumors occurring in the region of the pulmonary apex: further observations with report of twelve additional cases." *Illinois Med J*, 1942. **81**: 21-29.

145. Stein, J.J., "Sudden compression injuries of the abdomen." *US Veterans Administration Medical Bulletin*, 1943. **20**: 6-7.

146. Stein, J.J., "Combat experiences in the Pacific areas." *US Veterans Administration Medical Bulletin*, 1944. **21**: 177-187.

147. "Justin John Stein", in *Who's Who in America*. 1980, Marquis Who's Who: Chicago. **2** 3160.

148. Allen, C.D., "Report of results obtained in 100 cases by intravenous injection of Mercurochrome." *US Veterans' Bureau Medical Bulletin*, 1925. **1**: 27-33.

149. Allen, C.D., "A further report on the use of Mercurochrome intravenously, with a review of its action in 151 cases." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 443-446.

150. Martin, A., "Hemolytic streptococcus bacteremia following empyema, with recovery." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 541-543.

151. Harris, R.L., "Mercurochrome treatment of a case of streptococcus viridans septicemia with recovery." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 413-415.

152. Foster, H.E., "Facts and fancies regarding Mercurochrome-220 Soluble." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 300-308.

153. Dowling, H.F., *Fighting infection: conquests of the Twentieth Century*. Cambridge, MA and London: Harvard University Press, 1977, 106.

154. Walker, J.B., "Late results of fractures of the long bones - a statistical study of World War cases - I." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 293-314.

155. Walker, J.B., "Late results of fractures of the long bones - a statistical study of World War cases - II." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 409-427.

156. Walker, J.B., "Late results of fractures of the long bones - a statistical study of World War cases - III." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 525-543.

157. Walker, J.B., "Late results of fractures of the long bones - a statistical study of World War cases - IV." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 651-657.

158. Caldwell, H., "Resume of treatment of 25 cases of diabetes mellitus with insulin." *US Veterans' Bureau Medical Bulletin*, 1925. **1**: 1-6.

159. Rogers, J.C., "Residuals of encephalitis lethargica." *US Veterans' Bureau Medical Bulletin*, 1925. **1**: 20-23.

160. Prince, L.H., "The blood vessels in tuberculosis: some aspects of the part played by the blood vessels in the dissemination of tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1925. **1**: 11-18.

161. Crichlow, R.S., "Treatment of Raynaud's Disease by negative pressure." *US Veterans' Bureau Medical Bulletin*, 1925. **1**: 14-17.

162. Bacon, H.P., "A study of Larson's Ring Test applied to 315 cases of pulmonary tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 56-60.

163. Prince, L.H. and Wight, T.H.T., "Adenocarcinoma - primary in the renal tubule." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 987-991, 1095-?

164. Enright, J.J., "A preliminary report on attempts at active immunization of guinea pigs by urinary antigens from cases of tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 357-361.

165. Josewich, A. and Grave, F., "Correlation of clinical and laboratory procedures in tuberculosis. I. The complement fixation test." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 346-356.

166. Wrenn, H.T., "Studies on the bactericidal properties in vitro of certain fatty oils irradiated with the quartz-mercury-vapor spectrum." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 898-910.

167. Armstrong, C.L., "Report of cases of leprosy with unusual manifestations." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 1248-1254.

168. Covey, C.B., "Notes on amnesia." *United States Veterans' Bureau Medical Bulletin*, 1927. **3**: 356-362.

169. Freed, H., Haley, S.W. and Stephenson, W.O., "Thoracotomy for empyema complicating pneumonia - analysis of end results in 100 consecutive cases." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 22-26.

170. Crouch, E.L., "Multiple sclerosis." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 839-845.

171. Denson, R.L., "Ancient Grecian, Etruscan and Roman dentistry." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 251-258.

172. Flowers, H.L., "A study of the emotions in psychotic patients (a report of the examination of 100 psychotic patients with the Pressey test)." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 309-321.

173. Rabinovitch, A. and Roberts, C.G., "A comparative study of the Kahn and complement fixation tests of spinal fluid." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 692-696.

174. Read, J.M., "Tetany from overbreathing." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 491-493.

175. Alvarez, R.S. and Wight, T.H.T., "The Gregerson Test." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 888-890.

176. Seymour, W.Y., "Julius Caesar, epileptic." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 266-272.

177. Teitelbaum, A.D., "Preliminary Report of Fifteen Cases of Sodoku Treatment of General Paralysis." *US Veterans' Bureau Medical Bulletin*, 1930a. **6**: 263-270.

178. Schelm, G.W., "Typhoid vaccine in the treatment of general paralysis of the insane." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 544-548.

179. Crouch, E.L., "Narcolepsy." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 371-377.

180. Wight, T.H.T. and Meehan, W., "Value of media containing certain iron compounds in differentiating the typhoid-colon group of organisms." *United States Veterans' Bureau Medical Bulletin*, 1930. **6**: 493-495.

181. Moss, E.S., "An improved method for staining tubercle bacilli in tissues cut by the frozen section method." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 590-595.

182. Lasche, P.G. and Rubin, H., "Carbon dioxide-oxygen inhalations in catatonic dementia praecox." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 1037-1041.

183. Brown, C.P. and Gemar, F., "Experiments on bacteriophage adsorption by vulnerable bacteria." *US Veterans Administration Medical Bulletin*, 1931. **7**: 224-229.

184. Rothrock, A.M., "Medical science in the thirteenth century." *US Veterans Administration Medical Bulletin*, 1931. **7**: 1005-1009.

185. Mella, H., "The Use of Subarachnoid Lavage and Ethylhydrocupreine in Meningitis." *United States Veterans' Bureau Medical Bulletin,* 1931a. **7**: 77-78.

186. Fisher, S.G., "Stramonium in encephalitis." *US Veterans Administration Medical Bulletin,* 1931. **7**: 379-382.

187. Burkett, J.A., "Bronchial spirochetosis, with report of a case." *US Veterans Administration Medical Bulletin,* 1932. **8**: 26-37.

188. Wight, T.W.T., "A world's record for the transportation of Entamoeba Histolytica." *US Veterans Administration Medical Bulletin,* 1932. **8**: 306-307.

189. Terry, M.C. and Hollingsworth, E.W., "Elliptical human erythrocytes: report of two cases." *US Veterans Administration Medical Bulletin,* 1932. **9**: 7-17.

190. Terry, M.C., Hollingsworth, E.W. and Eugenio, V., "Elliptical human erythrocytes: report of two cases." *Arch Path,* 1932. **13**: 193-206.

191. Sanders, A.O., "Observations of heart action under vagus stimulation." *US Veterans Administration Medical Bulletin,* 1931. **7**: 212-217.

192. Garrett, G.H., "Pulmonary tuberculosis complicated by syphilis." *US Veterans' Bureau Medical Journal,* 1925. **1**: 1-9.

193. Kennedy, J.A., "Psychosis with alcoholic pellagra." *US Veterans Administration Medical Bulletin,* 1933. **10**: 155-158.

194. Monat, H.A., "An unusual case of hysteria with a retrocursive gait." *US Veterans Administration Medical Bulletin,* 1934. **11**: 167-168.

195. Cullins, J.G., Morgan, H.P. and Seymour, W., "Super-diathermy in the treatment of dementia paralytica." *US Veterans Administration Medical Bulletin,* 1935. **11**: 217-222.

196. Broglum, F.L., "Nineteen cases of pneumonia in members of the Civilian Conservation Corps with no deaths." *US Veterans Administration Medical Bulletin,* 1935. **11**: 258-261.

197. Smith, A.P., "Brain abscess consequent to latent head trauma." *US Veterans Administration Medical Bulletin,* 1935. **11**: 337-339.

198. Woldenberg, S.C., "Sulphur (colloidal) therapy in the treatment of arthritis." *US Veterans Administration Medical Bulletin,* 1935. **12**: 10-26.

199. Bogen, E.F., "Effects of long hospitalization on psychotic patients." *US Veterans Administration Medical Bulletin,* 1936. **12**: 345-353.

200. Carlisle, C.L. and Hecjer, C.H., "Use of benzedrine sulphate in catatonic stupors: case reports." *US Veterans Administration Medical Bulletin*, 1937. **13**: 224-227.

201. Woodward, F.A., "Molokai and its leper colony." *US Veterans Administration Medical Bulletin*, 1937. **14**: 60-61.

202. Baganz, C.N. and Laxson, G.O., "Hypoglycemic shock therapy in schizophrenia: results of treatment of six patients." *US Veterans Administration Medical Bulletin,* 1938. **14**: 301-305.

203. McClintock, H.A., "Experience with the insulin therapy of schizophrenia." *US Veterans Administration Medical Bulletin*, 1939. **16**: 97-105.

204. Carlisle, C.L., "Bacteriological examination of eating utensils." *US Veterans Administration Medical Bulletin*, 1939. **15**: 294-296.

205. Lasche, P.G., "Herpes zoster in early syphilis." *US Veterans Administration Medical Bulletin*, 1940. **16**: 253-256.

206. Haynes, H.J., "The treatment of schizophrenia with desoxycorticosterone acetate." *US Veteran Administration Medical Bulletin*, 1941. **18**: 141-147.

207. Bernard, L.J., "The status of thyroid ablation for intractable heart disease." *US Veterans Administration Medical Bulletin*, 1941. **17**: 336-342.

208. Matz, P.B., "Research projects." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 622-623.

209. Matz, P.B., "Research." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 1005-1007.

210. Ijams, G.E., "Address of the director to the 12th conference of the Medical Council." *US Veterans' Bureau Medical Bulletin*, 1931. **7**: 701-703.

211. "Report of Conference on Establishment of Research Units in Cardiovascular and Neuropsychiatric Disease." Typewritten, 1935.

212. "Conference on Medical Research." *US Veterans Administration Medical Bulletin*, 1936. **13**: 326-327.

213. "Medical Research Unit at Northport." *US Veterans Administration Medical Bulletin*, 1936. **13**: 327.

214. Scott, H., "Treatment of cancer at Edward Hines, Jr., Facility, Hines, Ill." *US Veterans Administration Medical Bulletin*, 1935. **12**: 1-9.

215. Owen, S.E., "The biologic diagnosis of teratoma testis." *J Lab Clin Med*, 1934. **20**: 296-301.

216. Owen, S.E., "Small animal metabolism cage." *J Lab Clin Med*, 1934. **19**: 1135-1137.

217. Cutler, M. and Owen, S.E., "Clinical value of Prolan A determinations in teratoma testis." *Am J Cancer*, 1935. **24**: 318-325.

218. Owen, S.E. and Cutler, M., "Diagnosis of teratoma testis by biologic assay of prolans." *US Veterans Administration Medical Bulletin*, 1937. **14**: 1-5.

219. Fortner, H.C. and Owen, S.E., "Chorionepithelioma in the male." *Am J Cancer*, 1935. **25**: 89-97.

220. Christoffersen, W.G. and Owen, S.E., "Neoplasms in cryptorchids." *Am J Cancer*, 1936. **26**: 259-268.

221. Owen, S.E. and Cutler, M., "Comparison of prolan bioassays in teratoma and other conditions." *Am J Med Sci*, 1936. **192**: 61-67.

222. Owen, S.E. and Cutler, M., "Sex hormones and prostatic pathology." *Am J Cancer*, 1936. **27**: 308-315.

223. Owen, S.E., "The reaction of fish to sex hormones." *Endocrinol*, 1936. **20**: 214-218.

224. Owen, S.E., "The Bitterling fish response to male sex hormones." *Endocrinol*, 1937. **21**: 689-690.

225. Owen, S.E., Polanco, Q.G. and Prince, L.H., "Urine chemistry in the diagnosis of embryonal tumors." *Am J Cancer*, 1937. **31**: 613-617.

226. Owen, S.E., "Sulphydryl and radon induced necrosis." *Growth*, 1937. **1**: 130-134.

227. Owen, S.E., "Sulphur and growth stimulation (a consideration of larval preparations)." *Growth*, 1938. **2**: 355-361.

228. Owen, S.E., "The action of growth stimulants on proteins." *Growth*, 1940. **4**: 135-137.

229. Owen, S.E., "Sex hormones, carcinogenics and sterols." *Quarterly Rev Biology*, 1937. **12**: 340-347.

230. Owen, S.E., "The genesis of cancer." *Mil Surg*, 1938. **82**: 218-225.

231. Owen, S.E., Weiss, H.A. and Prince, L.H., "Carcinogens and growth stimulation." *Science*, 1938. **87**: 261-262.

232. Owen, S.E., Weiss, H.A. and Prince, L.H., "Carcinogens and planarian tissue regeneration." *Am J Cancer*, 1939. **35**: 424-426.

233. Owen, S.E. and Williams, A.E., "Irradiation and hereditary mammary cancer." *Radiology*, 1940. **34**: 541-544.

234. Allaben, G.R. and Owen, S.E., "Adenocarcinoma of the breast coincidental with strenuous endocrine therapy." *JAMA*, 1939. **112**: 1933-1934.

235. Telephone interview with Robert Schrek, M.D., May 8, 1988.

236. Schrek, R., "Effect of pH on heat inactivation of tetanolysin." *J Immun*, 1933. **25**: 183-197.

237. Schrek, R., "A quantitative study of the growth of the Walker rat tumor and the Flexner-Jobling rat carcinoma." *Am J Cancer*, 1935. **24**: 807-822.

238. Schrek, R., "A comparison of the growth curves of malignant and normal (embryonic and post-embryonic) tissues of the rat." *Am J Path*, 1936. **12**: 515-530.

239. Schrek, R., "A biological method for sterilizing contaminated transplantable tumors." *Am J Path*, 1936. **12**: 531-543.

240. Schrek, R., "Further quantitative methods for the study of transplantable tumors. The growth of R39 sarcoma and Brown-Pearce carcinoma." *Am J Cancer*, 1936. **28**: 345-363.

241. Schrek, R., "The effect of the size of inoculum on the growth of transplantable rat tumors." *Am J Cancer*, 1936. **28**: 364-371.

242. Schrek, R., "Permanent and transient (fortuitous) variations of the growth components of transplantable rat tumors." *Am J Cancer*, 1936. **28**: 372-388.

243. Schrek, R., "A method for counting the viable cells in normal and in malignant cell suspensions." *Am J Cancer*, 1936. **28**: 389-392.

244. Schrek, R. and Avery, R.C., "Histologic observations on transplantable rat and rabbit tumors cultivated in the chorio-allantoic membrane of chick embryos, with special reference to the Walker rat tumor 256." *Am J Path*, 1937. **13**: 45-55.

245. Schrek, R. and Gates, O., "Cutaneous carcinoma I. A statistical analysis with respect to the duration and site of the tumors and the age of the patients at onset and at biopsy of tumor." *Arch Pathology*, 1941. **31**: 411-421.

246. Schrek, R., "Cutaneous carcinoma II. A statistical analysis with respect to measures of innate and clinical malignancy." *Arch Pathology*, 1941. **31**: 422-433.

247. Schrek, R., "Cutaneous carcinoma III. A statistical analysis with respect to site, sex and preexisting scars." *Arch Pathology*, 1941. **31**: 434-448.

248. Schrek, R., "A nomogram for determining the statistical significance and the probable error of differences of percentages." *J Lab Clin Med*, 1939. **25**: 180-184.

249. Schrek, R., "Logarithmic frequency distributions." *Human Biology*, 1941. **13**: 1-22.

250. Schrek, R., "Logarithmic correlation coefficients and regression equations." *Human Biology*, 1942. **14**: 95-103.

251. Schrek, R., "Operation of the Tumor Clinic at Hines, Ill., during the calendar year 1941." *US Veterans Administration Medical Bulletin*, 1943. **20**: 181-186.

252. Schrek, R., "Studies in vitro on the physiology of normal and cancerous cells I. The effect of high temperature and of moccasin venom on the viability of rabbit lymphocytes and polymorphonuclear leukocytes as determined by the method of unstained cell counts." *Arch Path*, 1943. **35**: 857-868.

253. Schrek, R., "Studies in vitro on the physiology of normal and cancerous cells II. The survival and the glycolysis of cells under aerobic and under anaerobic conditions." *Arch Path*, 1944. **37**: 319-327.

254. Schrek, R., "Studies in vitro on physiology of cells: effect of anisotonic solutions." *Proc Soc Exp Biol Med*, 1944. **57**: 348-351.

255. Schrek, R., "Studies in vitro on physiology of cells: histologic reactions of living tissues to hypotonic solutions." *Am J Path*, 1945. **21**: 1101-1119.

256. Schrek, R., "Radiosensitivity of lymphocytes and granulocytes in vitro according to the method of unstained cell counts." *Proc Soc Exp Biol Med*, 1945. **58**: 285-286.

257. Schrek, R., "A method for mounting gross pathologic specimens in Petri dishes." *J Lab Clin Med*, 1944. **29**: 91-96.

258. Schrek, R. and Allaben, G.R., "Statistical analysis of 2407 admissions to the Tumor Clinic of Veterans Hospital, Hines, Illinois, during 1943." *Cancer Res*, 1945. **5**: 539-546.

259. Schrek, R., "Cutaneous carcinoma IV. Analysis of 20 cases in Negroes." *Cancer Research*, 1944. **4**: 119-127.

260. Schrek, R., "The racial distribution of cancer I. Epithelial tumors of the skin, lip and breast." *Cancer Research*, 1944. **4**: 433-437.

261. Schrek, R., "The racial distribution of cancer II. Tumors of the kidney, bladder and male genital organs." *Ann Surg*, 1944. **120**: 809-812.

262. Schrek, R., Baker, L.A., Ballard, G.P. and Dolgoff, S., "Tobacco smoking as an etiologic factor in disease. I. Cancer." *Cancer Research*, 1950. **10**: 49-58.

263. Advisory Committee to the Surgeon General, *Smoking and Health*. Washington, DC: Public Health Service, 1964, 152 and p. 252.

264. Schrek, R., "Studies in vitro on physiology of cells: histologic reactions of living tissues to hypotonic solutions." *Am J Path*, 1945a. **21**: 1101-1119.

265. Schrek, R., "Studies in vitro on cellular physiology: the effect of X-rays on the survival of cells." *Radiology*, 1946. **46**: 395-410.

266. Schrek, R. and Donnelly, W.J., ""Hairy" cells in blood in lymphoreticular neoplastic disease and "flagellated" cells of normal lymph nodes." *Blood*, 1966. **27**: 199-211.

267. Lazell, E.W., "The group psychic treatment of dementia praecox by lectures in mental reeducation." *US Veterans Bureau Medical Bulletin*, 1930. **6**: 733-747.

268. Lazell, E.W., "The mechanism of psychic regression." *US Veterans Bureau Medical Bulletin*, 1927. **3**: 1089-1104.

269. Lazell, E.W., *The anatomy of emotion: man's two natures*. Vol. 3. New York and London: The Century Co., 1929, 267.

270. Lazell, E.W., "A study of the causative factors of dementia praecox: the influence of the blood and serum on embryological cells, a preliminary report." *United States Veterans' Bureau Medical Bulletin*, 1929. **5**: 40-41.

271. Lazell, E.W., "Sensitization in the convulsive states with special reference to heterophile antigen: I. Heterophile hemolysis." *J Lab Clin Med*, 1938. **23**: 1160-1184.

272. Lazell, E.W., "The Forssman or heterophile antigen." *US Veterans Bureau Medical Bulletin*, 1932. **8**: 477-485.

273. Lazell, E.W., "Sensitization in the convulsive states with special reference to heterophile antigen: I. Heterophile hemolysis." *J Lab Clin Med*, 1938. **23**: 1161.

274. Lazell, E.W., "The influence of heterophile antigen in nervous and mental disease." *US Veterans Bureau Medical Bulletin*, 1940. **16**: 235-252, 353-370.

275. "Hypoglycemic treatment of schizophrenia." *US Veterans Bureau Medical Bulletin*, 1937. **14**: 94-96.

276. Lazell, E.W., "The treatment of hay fever and ivy poisoning by local desensitization with sodium oleate and salts of other unsaturated fatty acids." *US Veterans Bureau Medical Bulletin*, 1938. **14**: 216-219.

277. "Messinger, Emanuel", in *Directory of Medical Specialists, Volume 12*, Marquis - Who's Who: Chicago 1535.

278. Messinger, E., "The estimation of cardiac function by simple clinical methods." *Ann Int Med*, 1937. **10**: 986-999.

279. Messinger, E., "Cardiovascular changes associated with the insulin shock treatment." *Ann Int Med*, 1938. **12**: 853-865.

280. Messinger, E. and Moros, N., "Cardiovascular effects of large doses of metrazol as employed in the treatment of schizophrenia." *Ann Int Med*, 1940. **13**: 1184-1204.

281. "New Neuropsychiatric Research Unit at Northport." *US Veterans Administration Medical Bulletin*, 1941. **18**: 225.

282. Roberts, C.S., "Follow-up report of 74 patients treated by pharmacologic shock compared with matched controls." *US Veterans Administration Medical Bulletin*, 1942. **19**: 49-59.

283. Moros, N., "The Alcoholic personality: a statistical study." *Quarterly Journal of Studies on Alcohol*, 1942. **3**: 45-49.

284. Turner, W.J., "Some dynamic aspects of alcoholic psychoses." *Am J Psychiatr*, 1942. **99**: 252-254.

285. Moros, N., "Factors in the development of general paralysis." *US Veterans Administration Medical Bulletin*, 1943. **20**: 196-201.

286. Huddleson, J.H., "Note on psychoses and psychoneuroses with malaria." *US Veterans Administration Medical Bulletin*, 1944. **21**: 1-4.

287. Turner, W.J., "A year's experience with electroencephalography." *US Veterans Administration Medical Bulletin*, 1944. **20**: 239-245.

288. Turner, W.J. and Roberts, C.S., "An adhesive nondrying electrode paste." *J Lab Clin Med*, 1944. **29**: 81.

289. Turner, W.J., Kress, B.H. and Harrison, N.B., "Determination of dihydroxyacetone in blood." *J Biol Chem*, 1943. **148**: 581-584.

290. Roberts, C.S., Turner, W.J. and Huddleson, J.H., "Variations of blood diastase and glucose in depression." *J Nerv Ment dis*, 1944. **99**: 250-255.

291. Turner, W.J., Lowinger, L. and Huddleson, J.H., "The correlation of pre-electroshock electroencephalogram and therapeutic result in schizophrenia." *Am J Psychiatr*, 1945. **102**: 299-300.

292. Huddleson, J.H. and Lowinger, L., "Note on initial and succeeding voltages to obtain grand mal in electroshock therapy." *J Nerv Ment Dis*, 1945. **102**: 191-193.

293. Turner, W.J., "A note on a mechanism of arterial rupture in cerebral arteriosclerosis." *J Neuropath and Exp Neurol*, 1946. **5**: 168.

294. Huddleson, J.H. and Gordon, H.L., "Fractures in electroshock therapy as related to roentgenographic spinal findings." *Military Surgeon*, 1946. **98**: 38-39.

295. Lowinger, L. and Huddleson, J.H., "Complications in electric shock therapy." *Am J Psychiatr*, 1946. **102**: 594-598.

296. Reisinger, J.A., "Study of hypertension in veterans." *Ann Int Med*, 1937. **10**: 1371 - 1389.

297. Reisinger, J.A. and Wilcox, B.B., "Heart weight and the measurement of the cardiac silhouette." *US Veterans Administration Medical Bulletin*, 1938. **15**: 108-117.

298. Reisinger, J.A., "Statistical study of heart diseases." *US Veterans Administration Medical Bulletin*, 1939. **16**: 33-44.

299. Reisinger, J.A. and Wilcox, B.B., "Statistical study of heart diseases." *US Veterans Administration Medical Bulletin*, 1942. **18**: 351-362.

300. Traum, A.H., "An etiologic study of 1036 cases of organic heart disease." *US Veterans Administration Medical Bulletin*, 1944. **20**: 377-388.

301. Reisinger, J.A., "The determination of exercise tolerance by the two-step test." *Am Heart J*, 1938. **15**: 341-353.

302. Reisinger, J.A., "The cold-pressor test." *Med Ann District of Columbia*, 1941. **10**: 381-386.

303. Reisinger, J.A., "Dissecting aneurysm of the aorta." *Arch Int Med*, 1940. **65**: 1097-1115.

304. "Article by John A. Reisinger." *US Veterans Administration Medical Bulletin*, 1940. **17**: 195.

305. Reisinger, J.A., Pekin, T.J. and Blumenthal, B., "Primary tumor of the inferior vena cava and heart with hemopericardium and alternation of the ventricular complexes in the electrocardiogram." *Ann Int Med*, 1942. **17**: 995-1004.

306. Blumenthal, B., "Nonclinical features of coronary arteriosclerotic heart disease." *US Veterans Administration Medical Bulletin*, 1939. **16**: 45-52.

307. Blumenthal, B. and Reisinger, J.A., "Prodromal pain in coronary occlusion." *Am Heart J*, 1940. **20**: 141-159.

308. Blumenthal, B. and Reisinger, J.A., "Pain in coronary arteriosclerotic disease of the heart." *US Veterans Administation Medical Bulletin*, 1941. **18**: 166-172.

309. Reisinger, J.A., "Coronary arteriosclerosis and heart pain." *US Veterans Administration Medical Bulletin*, 1942. **19**: 127-133.

310. Howell, J.D., ""Soldier's heart": the redefinition of heart disease and specialty formation in early twentieth century Great Britain." *Medical History*, 1985. **Supplement No. 5**: 34-52.

311. Reisinger, J.A., "Neurocirculatory asthenia." *US Veterans Administration Medical Bulletin*, 1943. **20**: 8-20.

312. Mazer, M. and Reisinger, J.A., "The thiocyanates in the treatment of hypertension." *US Veterans Administration Medical Bulletin*, 1942. **19**: 42-48.

313. Mazer, M., "A simple method for measuring cardiac area from the orthodiagram." *Am Heart J*, 1942. **24**: 511-513.

314. Mazer, M. and Reisinger, J.A., "An electrocardiographic study of cardiac aging based on records at rest and after exercise." *Ann Int Med*, 1944. **21**: 645-652.

315. Mazer, M. and Reisinger, J.A., "Criteria for differentiating deep Q3 electrocardiograms from normal and cardiac subjects." *Am J Med Sci*, 1943. **206**: 48-53.

316. Mazer, M. and Wilcox, B.B., "A simple graphic method for measuring the area of the orthodiagram." *Am J Roentgenol*, 1944. **51**: 444-446.

317. Mazer, M., "Palindromic rheumatism." *JAMA*, 1942. **120**: 364-365.

318. Kistin, A.D. and Mazer, M., "Current practice in cardiovascular diseases: I. The treatment of acute myocardial infarction." *US Veterans Administration Medical Bulletin*, 1943. **19**: 369-384.

319. Mazer, M. and Kistin, A.D., "Current practice in cardiovascular diseases: I. The use of digitalis." *US Veterans Administration Medical Bulletin*, 1943. **19**: 247-264.

320. Traum, A.H. and Wilcox, B.B., "Cardiovascular disease among veterans of World War II: a survey of 19,870 cases." *N Eng J Med*, 1946. **234**: 82-86.

321. Traum, A.H. and Wilcox, B.B., "An analysis of one hundred and fifty cases of cardiovascular disease in World War II veterans." *Mil Surgeon*, 1945. **95**: 5-10.

322. Traum, A.H., "Arteriosclerotic and hypertensive heart disease with right axis deviation." *Am J Med Sci*, 1944. **208**: 355-360.

323. Traum, A.H., "Interauricular septal defect with mitral stenosis - Lutembacher's syndrome." *US Veterans Administration Medical Bulletin*, 1944. **20**: 274-276.

324. Yater, W.M., Traum, A.H., Brown, W.G., Fitzgerald, R.P., Geisler, M.A. and Wilcox, B.B., "Coronary artery disease in men eighteen to thirty-nine years of age." *Am Heart J*, 1948. **36**: 334-372; 481-526; 683-722.

325. Kistin, A.D., "Simple manual cassette changer for multiple exposures in angiocardiography." *Am J Roentgen*, 1951. **65**: 615-618.

326. Kistin, A.D., Brill, W.D. and Robb, G.P., "Normal esophageal and gastric electrocardiograms: description, statistical analysis and bearing on theories of "electrocardiographic position"." *Circulation*, 1950. **2**: 578-597.

327. Kistin, A.D. and Robb, G.P., "Modification of the electrocardiogram of myocardial infarction by anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome)." *Am Heart J*, 1949. **37**: 249-257.

328. Kistin, A.D., "Observations on the anatomy of the atrioventricular bundle (Bundle of His) and the question of other muscular atrioventricular connections in normal human hearts." *Am Heart J*, 1949. **37**: 849-867.

329. Kistin, A.D. and Brill, W.D., "Clinically significant differences between precordial electrocardiograms derived from V and CF leads." *Ann Int Med*, 1950. **33**: 636-647.

330. Thompson, J.L. and Kistin, A.D., "Hoarseness in heart disease." *Ann Int Med*, 1948. **29**: 259-273.

331. Cooke, F.N., Evans, J.M., Kistin, A.D. and Blades, B., "An anomaly of the pulmonary veins." *J Thor Surg*, 1951. **21**: 452-459.

332. Kistin, A.D. and Landowne, M., "Analysis of retrograde conduction to the aorta from premature ventricular contractions, a common occurrence in the human heart." *Fed Proc*, 1950. **9**: 71-72.

333. Kistin, A.D. and Landowne, M., "Retrograde conduction from premature ventricular contractions, a common occurrence in the human heart." *Circulation*, 1951. **3**: 738-751.

334. Landowne, M. and Kistin, A.D., "The diagnosis of ventricular aneurysm. A study of certain clinical and dynamic features." *J Lab Clin Med*, 1950. **36**: 847-848.

335. Telephone interview with Milton Landowne, M.D., June 25, 1997.

336. "Proceedings of the Thirteenth Conference of the Medical Council, Veterans Administration." October 12-13, 1939. Washington, DC, 1939, 37.

337. "Proceedings of the Thirteenth Conference of the Medical Council." October 12-13, 1939, 1939, 27-29.

338. "Proceedings of the Thirteenth Conference of the Medical Council." October 12-13, 1939, 1939, 43-44.

339. "Proceedings of the Thirteenth Conference of the Medical Council." October 12-13, 1939, 1939, 40.

340. Adkins, R.E., *Medical Care of Veterans*. 1967, 170-171.

341. Magnuson, P.B., *Ring the Night Bell*. Birmingham, AL: Little, Brown&Company, reprinted by University of Alabama Press, 1986, 1960, 303.

342. Letter from Ray Lyman Wilbur, M.D. to E.O. Crossman, M.D., written at Palo Alto, CA, October 7, 1924.

343. Maisel, A.Q., "The veteran betrayed: how long will the Veterans' Administration continue to give third-rate medical care to first-rate men?" *The Reader's Digest*, April, 1945, 45-50.

344. Letter from Ray Lyman Wilbur, M.D. to Albert Q. Maisel, written at Palo Alto, CA, November 21, 1944.

345. Letter from Frank T. Hines to Ray Lyman Wilbur, M.D., written at Washington, DC, December 21, 1944.

(Intentionally Blank)

Section II. Beginnings of the Modern Program
1946-1953

(Intentionally Blank)

Chapter 3. Post-War Progress: Modern VA Research Begins

From 1946 to 1953, the effects of World War II on medicine in general and VA in particular were notable. The war's impact on literally millions of people, and the concerted response of the world medical community to unprecedented new challenges, brought sweeping changes to the health care landscape. In America, huge numbers of returning Veterans already had pushed VA to its limits and beyond. The era would mark the transformation of the entire VA system, including the rebirth of a near-dormant medical research program.

From the pre-war, hospital-based research efforts—scattered randomly at sites where local interest and initiative provided the impetus—emerged a modest new intramural VA research program. As it gradually took form, initial efforts were made to establish an infrastructure from which coordinated initiatives could be directed. These formative years were marked by limited funding, demands upon hospital space for clinical needs, and creation of a new culture among practitioners striving to establish research as a formal part of the VA mission.

A key figure in the overall conversion of the agency was General Omar N. Bradley, who had been appointed by President Truman in 1945 as Administrator of Veterans Affairs. Bradley's enormous public persona had been earned largely on the battlefield. He was viewed, especially among the rank-and-file, as a soldier's soldier—someone who, despite his four stars, understood the basic needs of his troops. Given the enormous task at hand, Bradley's great credibility would be indispensable in earning the political support needed to push through legislation that would enable VA to measure up to public expectations.

Bradley immediately named Paul Hawley, M.D., to head the VA's Medical Department. Dr. Hawley had been Chief Surgeon of the European Theater of Operations, adding another dimension of direct familiarity with the medical needs of wounded and returning service personnel. Bradley and Hawley recruited more high-profile leadership with the naming of Paul Magnuson, M.D., as Assistant Chief Medical Director for Research and Education. A dynamic academic surgeon from Chicago, Magnuson was widely known among the leaders of the nation's medical schools, and became instrumental in associating VA medicine with these institutions.

The post-war restructuring of VA medicine

Between the two World Wars, VA medicine was a vigorous, ingrown, semi-military system, which published its own journal and had a modest in-house research program. However, budget cuts during the Great Depression and shortages during World War II took their toll in terms of staffing. During the first year of the war alone, VA lost 7,000 employees.[1]

Until the 1930s, most VA physicians were Veterans of World War I.[2] Most of the younger doctors hired after 1933 were drafted into World War II. As a result, VA's small, aging physician staff was severely overworked. For these and other reasons, VA had acquired a reputation for inferior medical care. During the war, Dr. Paul Magnuson, who later became the first Assistant Chief Medical Director for Research and Education, worried about the care of servicemen when the fighting was over:

> "As every doctor knew, and as we from Chicago could see for ourselves at the Veterans Administration's big Hines General Hospital west of town with its 3,253 beds, the Veterans Administration Medical Department was in a sad state of decay. Medical treatment was so far below standard that the newspapers were beginning to notice the smell. I didn't know it then, but before the war was over this thing was going to blow up into a first-class nationwide scandal of bad treatment, costly blunders and administrative incompetence."[3]

At war's end, VA was unable to cope with the huge numbers of returning ill and injured soldiers and sailors. Through 1945, some doctors assigned to VA by the Army and Navy helped, but in January 1946, VA had fewer than a thousand doctors to care for 100,000 patients.[4, 5] As Michael DeBakey, M.D., described the situation: "the VA, at the end of the War, was simply unable to take care of the wounded."[6] The same was true of those with illnesses resulting from their service in the war.

Establishment of the Department of Medicine and Surgery

In 1945, serious delays in appointing medical staff held back the rebuilding of the VA medical system. Young, qualified physicians being discharged from the military wanted to join VA; at the same time VA desperately needed them. As Magnuson said, "Doctors without patients, patients without doctors!"[7] A means was needed to free the hiring of doctors, dentists and nurses from Civil Service restrictions and delays.

From the beginning, VA staff and advisors had tried to establish a VA medical corps. Early on, Administrator Hines supported these efforts, but later he opposed them despite the many difficulties of using the Civil Service procedures to recruit physicians. Slow recruitment and laborious promotion procedures (in which Hines personally signed off on all promotion actions)[8] saved money, an important goal to him. Nevertheless, these delays prevented VA from responding rapidly to new demands for medical care. Also, the Medical Department didn't report directly to the Administrator. In Hines's opinion, the Medical Department was better at a lower level in the organization, where doctors could concentrate on professional work and not worry about non-medical aspects of running the hospitals.

Magnuson, Hawley and Bradley worked together to push the medical corps concept through the Congress. With Public Law 293, the Department of Medicine and Surgery (DM&S) was born. In supporting this action, Hawley told the Senate:

> "Unless (Public Law 293) is enacted into law at once, before the recess of Congress, the Medical Service of the Veterans Administration will suffer further grave consequences, which may be irreparable. In the interests of the thousands of disabled Veterans who have by their sacrifices earned better medical care than they are now receiving, I urge immediate action on this bill."[9]

Not surprisingly, the Civil Service leaders opposed the bill and urged the President not to sign, which would amount to a "pocket veto." In his autobiography, *Ring the Night Bell*, Magnuson gives a dramatic portrayal of the last-minute reprieve of Public Law 293, 79th Congress. According

to Magnuson, Truman signed the bill only after the *Washington Post* reported that the Civil Service Commission and Bureau of the Budget urged a Presidential veto.[10]

Figure 3.1. Magnuson, Bradley and Hawley, the architects of Public Law 293

Armed with freedom to hire physicians, improved salaries, and partnership with the nation's medical schools, the new Department of Medicine and Surgery prospered. Within six months, VA's full-time physician staff increased from 600 to 4,000,[11] not including the resident physicians assigned to VA after medical school affiliations had begun.

Affiliation with medical schools—the concept

The nation's medical schools helped to remedy the crisis in VA medicine. Affiliations with medical schools grew rapidly under Magnuson's leadership, and he is generally credited for having the vision to establish these partnerships. Two years before he joined VA, Magnuson had made just such a proposal to Administrator Hines:

> "[W]hen the Veterans Administration built or leased or otherwise created new hospitals to meet the tremendous need that was coming, it ought to put them near the established medical schools and make them teaching hospitals like Presbyterian and Belleview.... I suggested that the Veterans Administration arrange to have the deans of the medical schools staff the hospitals, putting in chiefs of service, residents and interns."[12]

But the concept of VA-medical school partnership was not unique to Magnuson. Renowned heart surgeon Michael DeBakey recalled in a recent interview that others shared the concept:

> "[O]ne of the ideas cropped up—I can't tell whose original idea it was because, you know, these things were talked back and forth, and I was participating in it—was to have the medical schools affiliated with VA. One of the reasons we talked about this was because we had various general hospital units in the Army that were sponsored by medical schools. In fact, my own school had a unit, Tulane, but you had the Harvard Unit, you had the Hopkins Unit, and so on."[6]

Others had similar ideas. In 1944, Dr. Roy Kracke, Dean of the Medical College of Alabama, wrote General Hines suggesting that a VA hospital be built in Birmingham and serve as a teaching

hospital for the medical college. Hines rejected this proposal as well as the concept of medical school affiliation.[13]

Medical school affiliations begin

Medical school affiliations began as soon as the legislation establishing DM&S came into effect. Under the new law, well-trained physicians leaving the military could now be hired as staff physicians in VA hospitals without delay. Dr. Magnuson, strongly supported by Generals Bradley and Dr. Hawley, who was a retired Major General, worked feverishly to invigorate the VA medical program with the help of medical schools. By early 1947, VA hospitals, which had no resident physicians in training before 1946, now boasted some 1,000 residents.[14]

VA physicians hired as a part of a medical school affiliation expected to do research as an integral part of their academic roles. This required that research be carried out in VA hospitals. However, most VA hospitals had no laboratories suitable for basic research.[15] The original concept of Magnuson, Hawley and their co-workers was that VA research would be primarily clinical. The new VA doctors, however, wanted to be first-class academic physicians; for many, that meant doing bench research.

The barriers to research were many: Hospitals had no research space, no research equipment and no technical staff. Existing regulations forbade accepting research support from any person or agency other than VA, which didn't even have a research budget.[8, 16] Hospital management was inexperienced in supporting research and didn't understand research and its benefits for their hospitals. There was little research tradition in many medical schools and none in most VA hospitals. On the other hand, the new Deans Committees were very active in fostering research programs.

Keeping all VA doctors well informed: the *Technical Bulletins*

After VA's *Medical Bulletin* stopped publication in 1944, VA was without an official journal. However, the new leadership wanted to keep the medical staff up-to-date about medicine, science and administration. Toward this end, between 1946 and 1955, the new DM&S published a series of *Technical Bulletins* intended to inform VA physicians about the latest research and clinical care. Arthur Walker, M.D. the talented Tuberculosis Service Research Chief, became the editor. While some *Technical Bulletins* were administrative, others contained a great deal of new medical information. Many were written by highly respected authorities (Appendix III). For example, Jay Shurley, M.D., who later became a Senior Medical Investigator, wrote a *Technical Bulletin* on insulin shock therapy. At that time, he was running a unit that was a leader in this kind of therapy. Louis Welt, M.D., and Donald Seldin, M.D. wrote on edema, and Welt also wrote about dehydration. J. H. Means, M.D. wrote a *Technical Bulletin* advocating radioiodine therapy for hyperthyroidism in 1946, when peaceful use of atomic energy was just beginning (Chapter 6). Exciting results of the first streptomycin trial (Chapter 5) were shared with VA staff in the *Bulletin* before being published elsewhere. Richard Ebert, M.D., wrote about measurement of cardiac output. Peter Florsheim, M.D., and George Thorn , M.D. wrote about adrenal cortical insufficiency in 1950, just when cortisone became available for treatment. Willem Kolff, M.D. wrote about

dialysis for renal failure, well before this was common practice. Also ahead of its time was a 1950 *Bulletin* on cardiac massage after operating room cardiac arrest.

American medical research in 1946

During World War II, the war effort stimulated medical research. At a national level, the Committee on Medical Research (CMR), an arm of the powerful Office of Science and Technology, the same governmental office that supervised atomic bomb development, coordinated wartime medical research. The CMR arranged for the National Research Council (NRC) of the National Academy of Sciences to manage peer review committees to help decide who should receive contracts for medical research. Military medicine made great strides, thanks to both CMR-coordinated research and a modern system of medical records.[6, 17] As Richard H. Shryock, M.D. wrote in 1947, "The American people have been slow in realizing the significance of basic research. It has taken time to build up the interest prerequisite to public support in a democracy."[18]

At the end of World War II, American medical research was still limited to a few institutions and a few dedicated investigators, frequently working with their own resources or private support.[19] It was only in 1946 that the National Institute for Health (NIH) (soon to be expanded to the National Institutes of Health) began a grants program and established its Division of Research Grants. Previously, all NIH research support, except for a small National Cancer Institute grants program, was intramural or contractual.[20] The entire 1945 NIH budget was only $180,000, but by 1947 it had shot up to $8 million.[21] Only a few medical schools had large research programs. Most medical research, in medical schools and elsewhere, was clinical in nature.[22]

Research leaders in the early post-war VA

As VA's first Assistant Chief Medical Director for Research and Education (ACMD/R&E), Magnuson headed up establishment of the Research and Education Service. Robert Kevan, a young officer who had planned to study hospital administration, became his executive officer in December 1945.[23, 24] In 1946, he recruited Edward Harvey Cushing, M.D., to be Chief of the Education Section[25] and in 1947, Louis Welt to be Chief of the Research Section. When Magnuson was promoted to Chief Medical Director in 1948, Cushing became ACMD/R&E. Cushing resigned in 1951 and was replaced by George Lyon, M.D., who continued as ACMD/R&E until 1956.

Figure 3.2. Paul Magnuson, M.D.

Paul Magnuson, M.D., the first ACMD/R&E (1945-1948)

Dr. Magnuson has been described by those who knew him as a "stormy petrel,"[8] a "whirling dervish,"[26] a "pistol" and a brilliant man who did a tremendous amount of work.[27] Robert Kevan, who was Magnuson's Administrative Officer, described him as a great man who was very blunt, forceful and driving. Magnuson knew what he wanted and would do almost anything to get it.

Figure 3.3. Robert Kevan

Kevan recalled that he was a wonderful man to work with. If you made the "right" decision, he would back you up. If you made the "wrong" decision, he would give you a hard time.[23, 24] Ralph Casteel, who succeeded Kevan in 1948, agreed. He recalled that Magnuson "preached that the best medicine was practiced by those who also taught and who explored new therapeutic modalities."

Figure 3.4. Ralph Casteel

Magnuson believed that "the fight against bureaucracy and bureaucratic thinking is never won." By his own admission, he was insubordinate: "I have never in my life worked for anybody but a patient."[28] As ACMD/R&E and later as Chief Medical Director, he worked tirelessly to set up and protect VA-medical school partnerships. Even after leaving VA in early 1951, he remained active. He was known to have contacted the White House when a new hospital was planned at a site other than the promised location.[29] Martin Cummings, M.D., recalled that it was actually Magnuson who

recruited him to come to Central Office as Director, Research Service, in 1953. Cummings's new boss, Dr. George Lyon, was taken by surprise.[30]

Magnuson was interested in all aspects of academic medicine, but most of his attention went to upgrading patient care and teaching programs. Cummings recalled that, when Magnuson and John Barnwell, M.D., visited his laboratory near the Atlanta VA Hospital in 1950, Barnwell stayed to discuss science while Magnuson went off to the hospital to see the clinical service.[30]

Edward Harvey (Pat) Cushing, M.D., the second ACMD/R&E (1948-1951)

Figure 3.5. E.H. (Pat) Cushing, M.D.

Cushing (Figure 3.5) was energetic, intelligent and well-educated.[31] An internist from Harvard Medical School, he had been in private practice in Cleveland before the War. He was a nephew of Harvey Cushing, the famous neurosurgeon, and was the fifth physician in his family line. According to Alfred H. Lawton, M.D., who was Research Chief under him, he was a delightful person who "ran the office as a committee."[16]

Cushing was a disciple of Magnuson. He stayed on about a year after Administrator Carl Gray fired Magnuson. When Cushing resigned in February 1952, his departure was abrupt and without warning.[8] Why he left is unclear, but his obituary says it was in protest.[32]

George Lyon, M.D., the third ACMD/R&E (1951-1956)

Cushing's successor as ACMD/R&E was George M. Lyon, M.D., who had been Special Assistant to the Chief Medical Director for Atomic Medicine and Chief of the Radioisotope Section of the Research and Education Service.

Dr. Lyon has been described as difficult to work with by some of his colleagues. Instead of pushing for budget increases, he would ask for three budgets: Plan A/reduction, Plan B/hold-even and Plan C/slight increase. He supported the entire research program, but paid special attention to the Radioisotope program he also headed.

Early Chiefs of the Research Section

Research program leadership fell first to Dr. Louis Welt,, a young Instructor of Medicine at Yale who was Chief of the Research Section from 1947 to 1948.[33] Welt was replaced by Alfred Lawton, dean of a two-year medical school in North Dakota.[16] After Lawton left in 1951, the position remained vacant for two years. During that time, John Nunemaker, M.D., who was later Director, Education Service, was Acting Chief for a few months, and he was followed by Arthur Abt, M.D.[34] Then the position was vacant until 1953, when Martin Cummings came to VA Central Office (VACO) (Chapter 7).

Louis Welt, M.D. (1947-1948)

As the first Chief of the Research Section (1947-1948), Welt was active in starting collaborative programs with the National Academy of Sciences (NAS). He also arranged contracts with medical school faculty to carry out clinical research of importance to the Veteran patient. Welt worked with the VA Construction Service to try to alter plans for new VA hospitals to include research laboratory space. He is remembered as bright, young and energetic. Magnuson hired him without concern for VA's usual recruitment processes.[23, 24, 35] After staying only about a year, Welt returned to Yale as an NIH fellow and later Assistant Professor. He subsequently moved to the University of North Carolina, where he rose to the position of Chairman of Medicine, and then he returned to Yale as Chairman of Medicine.[33] During the 1950s, he wrote two *VA Technical Bulletins* on fluid metabolism.[36, 37] At the time of his death in 1973, he was assisting NAS in beginning a review of the VA patient care program (Chapter 16).[38]

Alfred Lawton, M.D. (1948-1951)

Lawton had been Dean of the two-year medical school at the University of North Dakota. He recalled that he spent a large fraction of his Central Office time traveling about the country trying to start research laboratories. Two major problems were finding staff capable of doing research and finding appropriate space. As he recalled, money was not a problem; research funds were available for justifiable programs. He left VA in 1951 to start a medical research program for the Air Force.[39]

Figure 3.7. Alfred Lawton, M.D. (right), with Roger Egeberg, M.D., Chief of Medicine, West Los Angeles VA Hospital, 1949

Struggle for research space

Dr. Welt and his successor VACO Chiefs of Research made a major effort to insert research space into plans for the new VA hospitals being rapidly built to correct the national shortage of beds for Veterans. Most new hospital plans didn't include space for research or radioisotope laboratories. Sometimes plans could be changed before construction, but research space was generally inadequate. For years, hospitals had to be retrofitted for research. Given the limits of the VA construction system, research space was squeezed into places like renovated closets, garages, laundries and bathrooms. Since construction monies were hard to get, these laboratories were primarily built with operational monies, each project costing less than the $15,000 limit.[16] Despite these obstacles, Welt, Lawton and their successors and counterparts at hospitals succeeded in making the intramural program flourish. By 1952, VA had medical research programs at 66 hospitals, with 373 employees paid from money set aside for support of research.[40] In 1952, Harold F. Weiler joined the Central Office team, as Chief of the Research Laboratories Section, to spearhead the construction and furnishing of the needed laboratories.

Figure 3.8. Harold F. Weiler

A "Research Hospital" is built

An important exception to the neglect of research space construction was the opening in 1953 of the new Chicago VA Research Hospital, later called the Chicago Lakeside VA Medical Center. A Chicago consulting group considered the best hospital architects in the business designed it.[41] Unlike other new VA hospitals, it had an all-marble exterior. Magnuson worked on every aspect of design and construction and watched each step carefully. According to his Executive Assistant Ralph Casteel, Magnuson "knew every crack in the rails between Washington and Chicago" from his frequent overnight trips to see how the construction was going.[8] This hospital was designed for the most advanced patient care available, and an entire floor was devoted to research laboratories. Francis Haddy, M.D., one of the first three physicians to work there in 1953, recalled that while the hospital construction had been finished when he arrived, the hospital was empty. For the first few months, the three physicians who were there, together with a helpful supply officer, went through catalogs and ordered everything "from bedpans to the most sophisticated research equipment." Haddy remembers no budget restrictions; they could buy the best.[42]

Half of the research floor was devoted to the radioisotope laboratory. John A.D. Cooper, M.D., of the Northwestern University faculty, who had trained under Magnuson, worked with the architects

to design this laboratory and later became its Chief. Thus, cutting-edge radioisotope research and clinical care was available at Lakeside from the moment the hospital opened.[43]

Gifts for research get the green light

When the VA research program was reborn after World War II, VA scientists were not allowed to accept gifts for research. Dr. Cushing pushed a policy, announced January 18, 1952, that nongovernmental gifts could be received and placed in the General Post Fund if approved by the Chief Medical Director. Expenditures, however, must honor donor stipulations.[44]

When Dr. Lyon described the new policy to the Committee on Veterans Medical Problems, he noted that interagency transfer of funds at the Central Office was possible, but the U.S. Public Health Service did not transfer funds appropriated for research grants to VA. He also stated, "It is not the policy of VA to encourage VA personnel to seek funds from agencies other than VA for research."[45] The result was that there was no way that a VA person could get an NIH grant until that policy was changed in 1954 (Chapter 7).

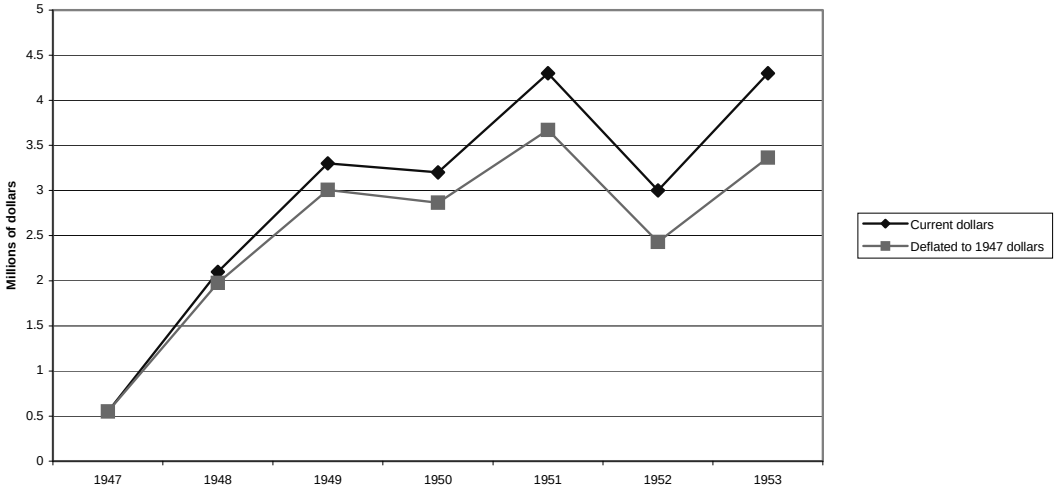
Cortisone research initiative

In 1950, Lawton negotiated with pharmaceutical company Merck and Co. to make more than 2,000 grams—said to be their entire supply—of the newly synthesized hormone cortisone available to VA for research. Twelve VA hospitals, including the Bronx; Chamblee, Ga; Cleveland, Ft. Hamilton, N.Y.; Ft. Logan (Denver), Colo.; Framingham, Mass.; Hines, Il.; Los Angeles, Minneapolis, Mt. Alto (Washington, DC), New Orleans and San Francisco, participated in cortisone studies. Their preliminary results were reported at a conference at Central Office in August 1950. Many leaders in VA research—among them, Solomon Papper, M.D., Marcus Krupp, M.D., Norman Shumway, M.D., Martin Cummings, M.D., Thaddeus Sears, M.D., William Adams, M.D., Ralph Goldman, M.D., James Halsted, M.D., Thomas Sternberg, M.D., William Merchant, M.D., Samuel Bassett, M.D., Louis Alpert, M.D., Hyman Zimmerman, M.D., Bernard Straus, M.D., Max Michael, M.D., James Hammarsten, M.D., and Maurice Strauss, M.D.[46]— presented basic and clinical papers. This conference stimulated further cortisone-related research, and two more conferences followed. This special program ended when the FDA approved cortisone for general clinical use.[16]

VA research funding, 1946-1952

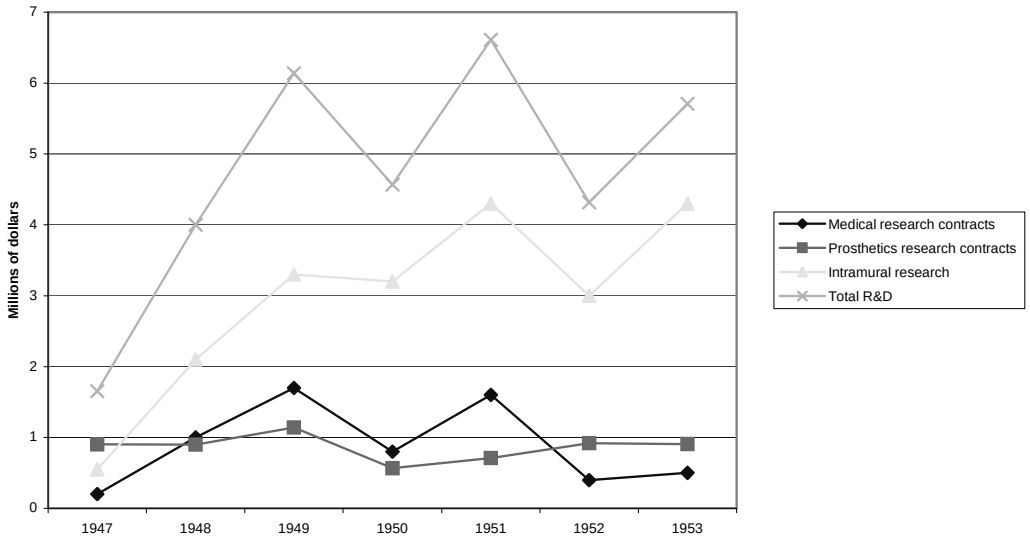
During this formative period from 1946 to 1952, the overall research budget grew only modestly (Figure 3.9).

Figure 3.9 Research budget, 1947-1953



Early on, the contract program grew, but later it declined as the intramural program began to solve its early problems and to reach "critical mass" (Figure 3.10).

Figure 3.10 R&D funds by program type, 1947-1953



Research sponsored by other units in DM&S

In addition to research leadership in the Research and Education Service, several other services identified research chiefs within their disciplines. Dr. K.R. Pfeiffer was Chief, Dental Research from 1949 until 1952. The Tuberculosis Service also had its Research Chief, Arthur Walker, who coordinated the early tuberculosis cooperative studies (Chapter 5).

Neuropsychiatry Service Research Chiefs for both Psychiatry and Psychology played key roles in launching the mental health research programs of the 1950s and 1960s. VA developed an active internship program early on for clinical psychology Ph.D. students, who were expected to produce research dissertations. Psychology leadership in Central Office actively encouraged research, and the Chief of Psychology Research, Maurice Lorr, M.D., reviewed all the resulting dissertations.[47]

While informal interaction occurred between these programs and people in the Research Service, there seems to have been no effort at that time to centralize the various research programs. Each Service operated independently and found the money to pay for the research it sponsored.

Six important research programs began during this early period, in addition to VA's formal intramural research program. Medical research contracts, the prosthetics research contracts and the Follow-up Agency—all undertaken in collaboration with the National Academy of Sciences—are discussed in Chapter 4. Chapters 5 and 6 describe the research sponsored by the Tuberculosis Service and the Atomic Medicine Section of the Research and Education Service. Important research begun within the Neuropsychiatry Service during this early period led to vigorous psychopharmacology studies of the late 1950s and 1960s, as discussed in Chapter 8.

Figure 3.11. Attendees at the 1952 VA Research and Education Conference

VA research conferences

In January 1951, Cushing and Lawton held a Medical Research Conference in Chamblee, Georgia. This began a series of conferences for VA research investigators that continued to be an important part of the research program until the late 1960s. Figure 3.11 shows the attendees gathered for the

second annual meeting in January 1952. In later years, these meetings became large and complex, with associated meetings of the radioisotope, tuberculosis and psychopharmacology groups.

Research in the hospitals

By 1948, a formal structure of local governance of the research programs in VA hospitals was in place.[48] Each hospital had a Research and Education Committee, consisting of Service Chiefs and two Deans Committee representatives. In a 1952 presentation to the Committee on Veterans Medical Problems, Dr. Lyon described the role of the Executive Secretary of the hospital Research Committee and announced that he was attempting to formalize that position at the hospital level as the Chief, Investigational Service.[40] By the late 1950s, this position was called the Associate Director of Professional Services for Research (ADPSR).[49] By 1961, the title of this research chief had been changed to Associate Chief of Staff for Research and Education (ACOS/R&E), and in 1972, it was once again changed, to Associate Chief of Staff for Research and Development (ACOS/R&D).

Even in 1946, many more small clinical studies were probably under way than those known to Central Office. The average VA intramural researcher was entrepreneurial and resourceful. Except for reporting their publications, which had to be approved by Central Office, they were more accountable to their local superiors than to Central Office. A few examples follow:

Salt Lake City VA Hospital

When Dr. John Nunemaker began as Chief, Medical Service, at the Salt Lake City VA Hospital in 1946, he used every means possible to start his research program. Most of the equipment he used belonged to the clinical laboratory. He established an animal facility in an old warehouse and raised rabbits on his farm and brought them in for experiments. For his bacteriological studies, he needed enriched serum and found that horse serum made a good medium. To obtain it, he would visit a slaughterhouse that prepared animal feed from horse meat. He would hold a bucket to collect the blood, which he anticoagulated to remove the red cells. He then let the serum clot and put it through a sausage grinder and then through a bacterial filter. The organisms grew well.[50] In the early 1950s, Nunemaker moved to VA Central Office, where he became Director, Education Service (Chapter 7).

Halloran VA Hospital and East Orange VA Hospital

Pathologist Oscar Auerbach, M.D., who worked at the Halloran VA Hospital in Staten Island New York from 1947 to 1952, used clinical facilities for his research studies. Auerbach recalled that he worked full time as a routine hospital pathologist and did his research between 4 and 6 a.m. and during evenings and weekends.[51] He moved to the new VA hospital in East Orange, N.J., in 1952. In the late 1950s, he carried out the work for which he is best known, showing smoking to be an important cause of lung cancer (Chapter 10). During the early post-war years, Auerbach's studies were primarily on the pathology of tuberculosis, although he also wrote on the germinal epithelium in male paraplegics,[52] hepatocellular carcinoma[53] and osteogenic sarcoma.[54] He collaborated with Gladys Hobby, Ph.D., then at Pfizer, Inc. but later at the East Orange VA Hospital, on animal studies aimed at developing an immunization method better than BCG for protection against

tuberculosis.[55] He reported a huge series of observations from autopsies at Seaview Hospital, a tuberculosis hospital on Long Island where he had worked before the war. He brought the material with him when he joined VA. From these records and slides, he extracted clinical information about rare complications of tuberculosis: 311 cases of tuberculous empyema,[56] 421 cases of tracheobronchial tuberculosis,[57] 108 cases of tuberculous meningitis[58, 59] and about 200 cases of serosal (pleural, peritoneal or pericardial) tuberculosis.[60] After streptomycin became available, he published on the ways that treatment with the antibiotic affects the pathology of tuberculosis.[61-63]

Oakland VA Hospital

Bruno Gerstl, M.D., also a pathologist, went to the Oakland VA Hospital in California (later moved to Martinez) in 1946 or 1947. The hospital, located in a renovated hotel, was loosely affiliated with the University of California at San Francisco. Gerstl collaborated with members of the Medical Service on clinical studies of mitral insufficiency,[64] erythrocyte fragility[65] and cryptococcosis.[66] In 1953, he and other pathologists reported on water, sodium and potassium contents of the human, guinea pig and rabbit lung.[67] Gerstl became interested in studying the immunology of cancer, for which needed, and eventually obtained, an animal room to house his guinea pigs. Gerstl also studied the immunology of tuberculosis, especially methods to measure tuberculosis antibodies.[68-70]

Figure 3.12. Bruno Gerstl, M.D., and Hospital Manager at the Oakland VA Hospital

Bronx VA Hospital

Bernard Roswit, M.D., Rosalyn Yalow, Ph. D., and Solomon Berson, M.D., were active in setting up a radioisotope unit and doing research using radioisotopes at the Bronx VA Hospital during this period. Their work is described in Chapter 11.

Ludwig Gross, M.D., was also active in research at this hospital, where he had transferred while still in uniform. During the time he could spare from his clinical duties, Gross was working in an old

bathroom. There, he bred leukemia-prone mice and tried to prove his theory of the viral cause of mammalian leukemia by transmitting this tendency to develop leukemia to normal mice. He finally succeeded in proving the theory in 1949.

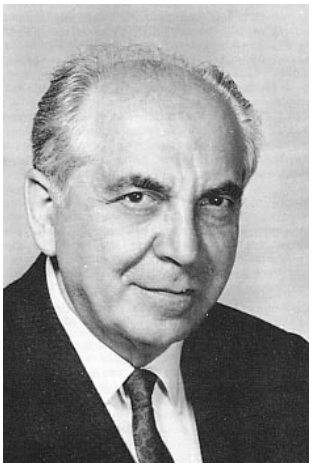


Figure 3.13. Ludwig Gross, M.D. (in 1975)

Gross was a war refugee from Poland. In 1939, he had given a lecture at NIH in which he speculated that leukemia was caused by a virus and that some day we would have a vaccine for it. He was introduced at that time to the Surgeon General and to the nucleus of the NIH staff. He then returned to Europe and was in Poland when the Nazis invaded. He escaped just in front of the Nazi line.

When, after many difficulties, he managed to return to the United States, he applied for a commission in the U. S. Army. At first he was turned down because he was not a citizen. He went to the Polish Ambassador, who wrote a letter that supported his entry into the U.S. Army Reserve in Cincinnati.

While in Cincinnati, Gross studied neuroblastoma, a condition that may skip a generation in its transmission. Gross considered that this might be due to vertical transmission of disease from generation to generation through the genome. This led to the concept that the virus responsible for the cancer transmission became associated with the genome. Not everyone carrying the genome developed cancer, since there was some mutual benefit between the genome and the virus.

Gross wanted to continue his research even after he entered active Army service. He wrote to John Joseph Bittner, Ph.D., the discoverer of a genetic line of mice that were very prone to breast cancer. He asked Bittner for a breeding pair of his mice and Bittner sent them. He had no laboratory, so he kept his mice in coffee cans covered with screens, in the trunk of his car and sometimes in his apartment.

In 1944, the Army transferred him to a station in North Carolina near Durham. While on leave, he went to Philadelphia, where he visited Baldwin Lucke, M.D.,who was working on transmission of kidney cancer in frogs. They discussed the problem of viral transmission. When Lucke went with

him to his car, Gross opened the trunk and showed him his mice. Lucke was a consultant to the Surgeon General, and one week after this meeting, Gross received transfer orders to the Bronx VA Hospital.

When he arrived at the Bronx, they told him to look for a room where he could set up a lab. He found a room that was being used for storage of oxygen tanks, which contained two toilets. The hospital staff cleared it out, and the carpenters covered the toilets. There, he studied the hemolytic action of mouse mammary carcinoma filtrates and extracts on mouse erythrocytes[71, 72] and a similar effect of human cancer extracts on human erythrocytes.[73] He later continued his study of breast cancer transmission, examining possibly oncogenic particles in mouse and human breast milk.[74]

But Gross's main interest was leukemia, and all he had when he arrived at the Bronx were his mice with a 90 percent chance of developing breast cancer. Jacob Furth, M.D., at Cornell had a strain of leukemia-prone mice, the AK strain. When Gross asked Furth for a breeding pair, he gave him 11 of his AK mice. Gross bred the mice himself. While there was no specific money for research, the hospital allowed him to spend some of his time conducting his studies. He spent five years, 1944 to 1949, trying to transmit the tendency to leukemia to non-leukemia-prone mice by injection of filtrates. The hospital was considering taking away his research time and space, as he seemed to be nonproductive.

In 1949, Gilbert Dalldorf, M.D., gave a lecture at the hospital about the Coxsakie virus. He explained that it could be transmitted only in newborns. Before Dalldorf even finished the lecture, Gross ran out to his laboratory where he had some newborn normal mice. He injected them with cells from AK mice, and they developed leukemia.[75, 76] Later he found that he could also transmit leukemia with just a filtrate,[77] and that the effect extended into the next generation.[78] He characterized transmission of other viruses as well during this early period[79-82] and evolved a theory about the viral transmission of malignancies.[83, 84]

Figure 3.14. Laboratory in which Ludwig Gross carried out his original work on mouse leukemia

After Gross's success in transmitting leukemia through the newborn mice, the Hospital Director, Ralph G. Devoe, a retired general, became very supportive and gave him substantial space to support his research.

Gross had trained as a surgeon and had to learn experimental techniques from scratch. C.P. Rhodes, M.D., at Memorial Hospital adopted him as a friend and taught him a great deal about research. The man who made the filters that Gross was using also helped him to develop his techniques.[85]

While extreme, Gross's early experience at the Bronx VA Hospital exemplifies the determination and independence shown by many early VA researchers. They had little guidance and often were not well understood. Little or no research infrastructure was available. But a venturesome spirit that encouraged original thinking and inventiveness permeated the newly "academic" organization.

Washington, D.C., VA Hospital

Hyman Zimmerman, M.D., joined VA in 1949 at the old Mt. Alto (Washington, D.C.) Hospital and started a research laboratory there. He carried out the research himself, using clinical equipment and supplies, as well as some of his own funds. The question of getting money for research was not even raised; neither he nor anyone else even *thought* about asking for money to support his research. However, in 1951 he was recruited to the Omaha (Neb.) VA Hospital to be Chief of the Medical Service. Although he made the availability of a laboratory a condition of his recruitment, no research laboratory awaited him in Omaha. The Hospital Director contacted the Regional Director, and the Regional Director contacted Dr. Lawton. The princely sum of $25,000 was allocated to set up the new laboratory. There was no review of his research and, as he recalled, later support for his research came from the local hospital budget.[86]

West Los Angeles Wadsworth VA Hospital

Shortly after DM&S was established, the huge Wadsworth VA Hospital in Los Angeles formed a Dean's Committee that included leaders from both the University of Southern California (USC) and the College of Medical Evangelists, now Loma Linda School of Medicine. After faculty for the planned University of California at Los Angeles (UCLA) School of Medicine began to arrive, UCLA also sat on the Dean's Committee. B.O. Ralston, M.D., Dean of the School of Medicine at USC, was the Chairman. Ralston met Roger Egeberg, M.D., who had been General McArthur's personal physician during the war, in Washington, and recruited him to be Chief of Medicine at Wadsworth. Egeberg (Figure 3.7) arrived in July 1946 and began working with the "old guard" to try to upgrade the facility. Planning for the new UCLA School of Medicine was under way, and key faculty were being recruited. Until 1955, UCLA had no hospital, and many of the new faculty worked at Wadsworth.[87]

William Adams, M.D., arrived in Los Angeles in 1948 and joined the Wadsworth staff. Shortly thereafter, Adams and Ralph Goldman, M.D., began a multidisciplinary research effort. Once they had acquired laboratory space, they still lacked staff and funds to hire staff. Adams made two trips

to Washington, where he talked with Alfred Lawton. He presented Lawton with a proposed Table of Organization, and Lawton gave him funds to hire 14 or 15 technical staff in response to Adams's argument was that a staff of this size was needed to attract senior people. After that, it still took more than a year to get the lab set up.

Figure 3.15. Samuel Bassett, M.D.

Samuel Bassett, M.D., came to Wadsworth about 1950. Bassett was seen as instrumental in the discovery of potassium deficiency syndrome in corrected severe diabetic acidosis. Adams remembered a patient who had become paralyzed after treatment for diabetic acidosis. Bassett suggested that she might have a low blood potassium level. Adams ran the potassium measurement himself by a colorimetric method (flame photometry was not yet available). No one believed the results because they were so low. After the patient was given potassium, they were able to take her out of the respirator and she improved. The resident who wrote the paper received the credit for this important discovery.[88]

John Lawrence, M.D., the newly appointed Chairman of Medicine at UCLA, used money from Parke Davis Company to renovate four Quonset huts on the VA campus behind Building 114 for the use of the new UCLA faculty. These Quonset huts were empty, requiring that everything be installed including a heating system. The laboratory work benches were obtained free from the old chemistry building at the University, when a new chemistry building was built. A walk-in cold room was put in at a cost of $2,500. A weighing room had to be specially constructed, because the Quonset hut shook. To stabilize the balances, a concrete slab was laid through the floor.[89]

Egeberg's effort as Chief of Medicine was primarily to build the Medical Service and, incidentally, to protect his staff during the McCarthy era.[87] He wrote clinical papers even before there was a research laboratory at Wadsworth.[90, 91] His personal research interest was coccidioidomycosis. In addition to clinical treatment trials,[92, 93] he worked to find out where the coccidioidomycosis organism was when it was not in the human body. Dr. Ann Leconnen, who was in charge of the

Outpatient Department at the LA County General Hospital, collaborated on this project with Egeberg and his wife. They had collected just about everything they could find around the Lost Hills area, which is in a coccidioidomycosis endemic area. They were unable to culture the organism from any of the plants or soil or warm-blooded animals.

Thinking that a cold-blooded animal was a possible vector, the team decided to try to infect rattlesnakes with coccidioidomycosis organisms by having the snakes inhale the organisms. To obtain the snakes, Leconnen contracted with the owner of a small general store in the San Joaquin Valley. One evening after her children had gone to bed, the store owner came to her house carrying a gunny sack. He opened the gunny sack and dumped a dozen rattlesnakes on the floor.

To make the rattlesnakes inhale the suspension of coccidioidomycosis organisms, they found a resident who had been in the desert during his military service and had learned how to handle rattlesnakes. He would grasp the snake behind its head, causing it to expose its fangs. Venom would drop from the fangs. The snake would then hold its breath, often as long as five minutes. Holding a syringe full of the suspension of coccidioidomycosis organisms, Egeberg would wait in front of the snake, watching to see when it would take its first breath. When the snake finally breathed, he would empty the syringe into the snake's mouth, forcing it to inhale the organisms. Ultimately, the snakes failed to develop cocci, and the project was dropped.[94]

Ralph Goldman, M.D., who later entered the field of gerontology and headed VA's nationwide Extended Care program, was a nephrologist. In addition to clinical reports on hereditary hemorrhagic telangiectasis,[95] unsuccessful attempts to treat Hodgkin's Disease with aureomycin,[96] and acute renal failure due to phenylbutazone,[97] he took advantage of the metabolic unit he had helped to establish. There, he studied the diurnal variation in excretion of water, and electrolytes and steroids in congestive heart failure and hepatic cirrhosis.[98, 99] He also studied renal function in multiple myeloma, showing that reduction in glomerular, vascular and tubular function is parallel, consistent with destruction of entire nephron units.[100] With Bassett, he studied calcium and phosphorus excretion after calcium administration in patients with hypoparathyroidism and found a disproportionate increase in calcium excretion when serum calcium had normalized.[101] He also studied the mode of creatinine excretion in renal failure, excluding fecal excretion and increased creatine formation as alternative routes.[102]

Figure 3.16. Ralph Goldman, M.D.

Bassett collaborated widely, working in a metabolic unit at Wadsworth that Adams and Goldman established. Among his fellows was William Blahd, who later became a leader in nuclear medicine (Chapter 6). While working with Bassett, Blahd published an attempt to treat Hand-Schuller-Christian Syndrome with cortisone, apparently one of the cortisone studies begun by Dr. Alfred Lawton.[103] He demonstrated that prolonged epinephrine administration did not impair adrenal cortical function.[104] Blahd also carried out a study of potassium deficiency that was probably the trigger for his later extensive work on potassium metabolism.[105]

Seeking an alternative pathway for iron loss, William Adams performed an early study measuring iron excretion in sweat. He and his colleagues found that sweat itself contained no measurable iron, though the skin cells desquamated with the sweat were iron-rich.[106] He had a special interest in multiple myeloma patients, in whom he studied fibrin formation and the effects of plasmapheresis.[107, 108] With Bassett, he studied metabolic balance of calcium, phosphorus, electrolyes and nitrogen in multiple myeloma patients treated with ACTH, establishing the negative balances now recognized,[109] and the effect of cortisone and ACTH in leukemias of various types.[110]

With Melvin Levin, M.D., and others, Bassett also studied metabolism in gout, showing little effect of an acute gouty attack on adrenal function and equivocal therapeutic benefit from ACTH, cortisone and testosterone. The team found that therapeutic doses of colchicine were followed by sodium and chloride retention.[111, 112]

Atlanta VA Hospital

In Atlanta, internist Max Michael, M.D., studied the inflammatory response, with a special interest in sarcoidosis. His follow-up epidemiological study of 350 cases of sarcoidosis showed a predominance in persons who reside in the South and in rural areas.[113] He demonstrated delay in response to an inflammatory stimulus in rabbits treated with cortisone.[114]

In 1949, Martin Cummings, M.D., who had been Chief of the Tuberculosis Research Laboratory at the Communicable Disease Center in Atlanta, moved to the Atlanta VA Hospital as Chief of a new tuberculosis laboratory. He, Michael and Walter L. Bloom, M.D., collaborated on studies comparing macrophage response in peritoneal exudates in rats and rabbits in an attempt to explain the greater resistance of rats to tuberculosis[115] and the influence of cortisone in reducing the rat's natural resistance to experimental tuberculosis.[116] In other collaborations, Cummings expanded on the latter finding, showing that cortisone-enhanced tuberculosis in rats responded to streptomycin,[117] and that induction of diabetes with alloxan also made rats susceptible to virulent tuberculosis.[118] He and his collaborators also showed that ACTH and cortisone do not suppress the tuberculin reaction in guinea pigs,[119] that centrifugation is not an effective way to concentrate tubercle bacilli in sputum,[120] and that certain amino acids may enhance resistance to tuberculosis in a variety of animals.[121] Cummings and his coworkers also published clinical articles on the hemagglutinen test for tuberculosis,[122] methods of culture for the tubercle bacillus[123] and treatment of tuberculous meningitis.[124] After he moved to Central Office, Cummings collaborated with statistician Dorothy Livings on a report of the incidence of streptomycin-resistant tubercle bacilli in VA patients.[125]

Minneapolis VA Hospital

Dr. Richard Ebert had been stationed in Europe during World War II as part of a Harvard Medical School medical unit. There he met General Bradley. After the war, Ebert, who was looking for a job, was approached by Cecil Watson, M.D., Ph.D., Chairman of Medicine at the University of Minnesota. In February 1946, Ebert joined the Minneapolis VA Hospital as Chief of Medicine. At that time, the Dean's Committee was just beginning to be active. The hospital was generally very slow moving. The large Tuberculosis Service had many patients with long stays. In addition, demobilized service people demanded VA care.

With the backing of the Dean's Committee and of Central Office, Ebert rapidly built up the Medical Service. Within six months, a program of resident and medical student training was thriving.

Not long after that, Ebert and others began a research program. Watson and Morris Visscher, M.D., the Chairman of Physiology, were interested in VA. Visscher arranged for Herbert Wells, who was in the Department of Physiology but who had an M.D. degree, to join VA's patient care staff. They also recruited an equipment specialist to help them equip the research laboratories. The Minneapolis research program was becoming active, and they began to look for money. They contacted Central Office and were told to contact NIH, but then they learned that NIH policy was not to give grants to VA researchers. In about 1947, they were among the first to receive research money from VA.[126]

In 1947, Dr. Craig Borden, who later became Chief of Medicine at the Chicago Lakeside VA Hospital, and Ebert set up the first cardiac catheterization laboratory west of the Mississippi. It was an opportunity for both advanced patient care and clinical research. With this laboratory, they made some of the first circulatory measurements, such as measurements of pressures in the pulmonary circulation.[127, 128] They studied pulmonary hypertension,[129, 130] the anoxia of myocardial infarction,[131] and ventilation[132, 133] and lung elasticity in various clinical conditions.[134] In 1949, Ebert and Abraham Falk, M.D., reported in the *Journal of the American Medical Association* on 17

cases of tuberculous pericarditis treated with streptomycin in a cooperative clinical trial (Chapter 5) and found that circulatory failure was cured or much improved in eight of them.[135] With others, Ebert published an article in *Science* about erythrocyte disappearance kinetics in normal persons and in persons with hemolytic diseases.[136]

In late 1946, Ebert recruited William Tucker, M.D., from the University of Chicago to head the 200-bed Tuberculosis Service. Other key recruits were James Hammarsten, M.D., Benjamin Heller, M.D and Leslie Zieve, M.D. These physicians collaborated among themselves and with Ebert and others. Among their publications were studies of blood volume,[137, 138] reports on acceleration of liver disease in tuberculous patients treated with amithiozone,[139] the effects of cortisone in nephropathies[140] and adrenaline on renal function and electrolyte excretion.[141] Clinical reports included a 1949 compilation of the studies of streptomycin treatment methods up to that time[142] and case reports on acute myocarditis[143] and on transfusion reactions.[144]

Figure 3.17 Number of VA publications

VA research in the early 1950s

The intramural program quickly bore fruit. VA publications increased from fewer than 100 per year in 1945 and 1946 to more than 800 in 1951. Even without a mandate from the Congress (Chapter 7), more and more money was being spent on intramural research. VA was on its way to leadership in medical research.

References

1. Adkins, R.E., *Medical Care of Veterans*. Washington, D.C.: U.S. Government Printing Office, 1967, 166.

2. Interview with Abraham Gottlieb, M.D., December 18, 1991 at Palo Alto, CA VA Medical Center.

3. Magnuson, P.B., M.D., *Ring the Night Bell*. Birmingham, Ala: Little Brown and Company, 1960, 268.

4. Magnuson, *Ring the Night Bell*. 1960, 278.

5. Adkins, *Medical Care of Veterans*. 1967

6. Interview with Michael DeBakey, M.D., January 28,1994 at Dr. DeBakey's office at Baylor Medical Center, Houston, TX.

7. Magnuson, *Ring the Night Bell*. 1960, 276.

8. Interview with Ralph Casteel, May 3, 1988 at a restaurant in Bethesda, MD.

9. Adkins, *Medical Care of Veterans*. 1967, 211.

10. Magnuson, *Ring the Night Bell*. 1960, 289-298.

11. Adkins, *Medical Care of Veterans*. 1967, 214.

12. Magnuson, *Ring the Night Bell*. 1960, 269.

13. Adkins, *Medical Care of Veterans*. 1967, 181.

14. National Academy of Sciences - National Research Council. "Minutes of First Meeting, Committee on Veterans Medical Problems." September 20, 1946. Washington, D.C.: National Research Council, 1946, 2.

15. NAS-NRC. "Minutes, First Meeting of the CVMP." September 20, 1946, 1946, 2-3.

16. Telephone interview with Alfred H. Lawton, M.D., April 26, 1988.

17. Shryock, R.H., *American Medical Research, Past and Present*. New York: The Commonwealth Fund, 1947

18. Shryock, *American Medical Research*. 1947, 321.

19. Harvey, A.M., *Science at the Bedside. Clinical Research in American Medicine, 1905-1945*. Baltimore and London: Johns Hopkins University Press, 1981, 554.

20. Telephone interview with Ernest Allen, Ph.D., April 11, 1988.

21. McCarthy, C.R. "Testimony before the U.S. House of Representatives Committee on Veterans' Affairs." *Hearing on Government Sponsored Research involving Radioactive Materials Conducted in VA Medical Centers*. February 8, 1994. Washington, D.C., 1994, 4.

22. Harvey, *Science at the Bedside*. 1981

23. Magnuson, *Ring the Night Bell*. 1960, 285-286.

24. Telephone interview with Robert Kevan, January 11, 1992.

25. Magnuson, *Ring the Night Bell*. 1960, 306.

26. Magnuson, *Ring the Night Bell*. 1960, 320.

27. Interview with Dorothy Bluestein, May 5, 1992 at Ms. Bluestein's home in Silver Spring, MD.

28. Magnuson, *Ring the Night Bell*. 1960, 344.

29. Magnuson, *Ring the Night Bell*. 1960, 349-350.

30. Interview with Martin M. Cummings, M.D., February 7, 1994 at Dr. Cummings's home in Florida.

31. Interview with Marjorie T. Wilson, M.D., April 29, 1988 at Dr. Wilson's office at ECFMG, in Washington, D.C.

32. "Edward Cushing, District Physician." *The Washington Post*, Washington, D.C., November 16, 1969.

33. Louis Welt, M.D. Curriculum Vitae, provided by Yale University

34. National Academy of Sciences - National Research Council. "Minutes, Twenty fifth Meeting of the CVMP." December 5, 1952. Washington, D.C.: National Research Council, 1952, 17.

35. Interview with Gilbert W. Beebe, Ph.D., June 1, 1994 at a hotel lobby in Washington, DC.

36. Welt, L. and Seldin, D., "The pathologic physiology and treatment of edema." *Veterans Administration Technical Bulletin*, 1951. **10-69**.

37. Welt, L., "The pathogenesis and management of dehydration." *Veterans Administration Technical Bulletin*, 1955. **10-105**.

38. Interview with Richard Greene, M.D., Ph.D, April 7, 1993 at Dr. Greene's home in Washington, D.C.

39. National Academy of Sciences - National Research Council. "Minutes, Twenty first Meeting of the CVMP." May 25, 1951. Washington, D.C.: National Research Council, 1951, 10.

40. NRC. "Minutes, Twenty fifth Meeting of the CVMP." 1952, Appendix 2, p. 546.

41. Magnuson, *Ring the Night Bell.* 1960, 315-316.

42. Telephone interview with Francis Haddy, M.D., Ph.D., April 6, 1988.

43. Telephone interview with John A.D. Cooper, M.D., March 24, 1988.

44. NAS-NRC. "Minutes, Twenty fifth Meeting of the CVMP." December 5, 1952. Washington, D.C.: National Research Council, 1952, Appendix 2, 547.

45. NAS-NRC. "Minutes, Twenty fifth Meeting of the CVMP." December 5, 1952. Washington, D.C.: National Research Council, 1952, 548.

46. Lawton, A.H. "Veterans Administration Conference on Cortisone Research." 1950.

47. Interview with Maurice Lorr, Ph.D., April 28, 1994 at Dr. Lorr's office in Washington, D.C.

48. "Veterans Administration Technical Bulletin 10A-152: Medical research program."

49. Chapple, C., "Newsletter." *R and E Newsletter*, May, 1960, 2.

50. Telephone interview with John C. Nunemaker, M.D., January 14, 1992.

51. Interview with Oscar Auerbach, M.D., October 30, 1992 at Dr. Auerbach's office at the East Orange, NJ VA Medical Center.

52. Stemmerman, G., Weiss, L., Auerbach, O. and Friedman, "A study of the germinal epithelium in male paraplegics." *Am J Clin Path*, 1950. **20**: 24-34.

53. Auerbach, O. and Trubowitz, S., "Primary carcinoma of the liver with extensive skeletal metastasis and panmyelophthisis." *Cancer*, 1950. **3**: 837-843.

54. Auerbach, O., Friedman, M., Weiss, L. and Amory, H., "Extraskeletal osteogenic sarcoma arising in irradiated tissue." *Cancer*, 1951. **4**: 1095-1106.

55. Hobby, G., Lenert, T. and Auerbach, O., "The immunizing properties of an isoniazid-resistant mutant of the Vallee strain of M. Tuberculosis as compared with BCG." *Am Rev Tuberc*, 1954. **70**: 527-530.

56. Auerbach, O., "Empyema as a complication of chronic pulmonary tuberculosis." *Am Rev Tuberc*, 1949. **59**: 601-618.

57. Auerbach, O., "Tuberculosis of the trachea and major bronchi." *Am Rev Tuberc*, 1949. **60**: 604-620.

58. Auerbach, O., "Tuberculous meningitis: Correlation of therapeutic results with the pathogenesis and pathologic changes. I. General considerations and pathogenesis." *Am Rev Tuberc*, 1951. **64**: 408-418.

59. Auerbach, O., "Tuberculous meningitis: Correlation of therapeutic results with the pathogenesis and pathologic changes. II. Pathologic changes in treated and untreated cases." *Am Rev Tuberc*, 1951. **64**: 419-429.

60. Auerbach, O., "Pleural, peritoneal and pericardial tuberculosis." *Am Rev Tuberc*, 1950. **61**: 845-861.

61. Auerbach, O. and Stemmermann, G., "Anatomic change in tuberculosis following streptomycin therapy." *Am Rev Tuberc*, 1948. **58**: 449-462.

62. Stemmermann, G. and Auerbach, O., "Massive pulmonary hemorrhage in tuberculosis. A report of two unusual cases." *Am Rev Tuberc*, 1950. **62**: 324-330.

63. Auerbach, O., Katz, H. and Small, M., "The effect of streptomycin therapy on the broncho-cavitary junction and its relation to cavitary healing." *Am Rev Tuberc*, 1953. **67**: 173-200.

64. Movitt, E. and Gerstl, B., "Pure mitral insufficiency of rheumatic origin in adults." *Ann Int Med*, 1953. **38**: 981-1001.

65. Movitt, E., Gerstl, B. and McKinlay, E., "Osmotic erythrocyte fragility in patients with jaundice." *Am J Med Sci*, 1951. **222**: 535-537.

66. Berk, M. and Gerstl, B., "Torulosis (cryptococcosis) producing a solitary pulmonary lesion. Report of a four year cure with lobectomy." *J Am Med Assn*, 1952. **149**: 1310-1312.

67. Mendenhall, R.M., Ramorino, P.M. and Gerstl, B., "Water, sodium, and potassium content of human, guinea pig, and rabbit lung." *Proc Soc Exper Biol and Med*, 1953. **82**: 318-322.

68. Gerstl, B., Kirsh, D., Andros, E., Winter, J. and Kidder, L., "Evaluation of hemolytic modification of Middlebrook-Dubos test for tuberculosis antibodies." *Am J Clin Path*, 1952. **22**: 337-344.

69. Gerstl, B., Kirsh, D., Davis, W. and Barbieri, M., "Absence of circulating antibodies in patients with pulmonary tuberculosis." *Science*, 1954. **120**: 853-854.

70. Gerstl, B., Kirsh, D., Winter, J., Weinstein, S., Hollander, A., Cova, P. and Barbieri, M., "Nonspecific reactions with the Middlebrook-Dubos Test for tuberculosis antibodies." *J Lab Clin Med*, 1954. **44**: 443-448.

71. Gross, L., "Hemolytic action of mouse mammary carcinoma filtrate on mouse erythrocytes in vitro." *Proc Soc Exper Biol and Med*, 1947. **65**: 292-293.

72. Gross, L., "Increased hemolytic potency of mouse mammary carcinoma extracts following incubation with tumor cells." *Proc Soc Exper Biol and Med*, 1948. **67**: 341-343.

73. Gross, L., "Destructive action of human cancer extracts on red cells in vitro." *Proc Soc Exper Biol and Med*, 1949. **70**: 656-662.

74. Gross, L., Gessler, A. and McCarthy, K., "Electron-microscopic examination of human milk particularly from women having family record of breast cancer." *Proc Soc Exper Biol and Med*, 1950. **75**: 270-276.

75. Gross, L., "Suseptibility of suckling-infant, and resistance of adult, mice of the C3H and of the C57 lines to inoculation with AK leukemia." *Cancer*, 1950. **3**: 1073-1087.

76. Gross, L., "Susceptibility of newborn mice of an otherwise apparently "resistant" strain to inoculation with leukemia." *Proc Soc Exper Biol and Med*, 1950. **73**: 246-249.

77. Gross, L., "'Spontaneous' leukemia developing in C3H mice following inoculation, in infancy, with AK-leukemic extracts, or AK-embryos." *Proc Soc Exper Biol and Med*, 1951. **76**: 27-32.

78. Gross, L., "Pathogenic properties, and 'vertical' transmission of the mouse leukemia agent." *Proc Soc Exper Biol and Med*, 1951. **78**: 342-348.

79. Gross, L., "Presence of leukemic agent in normal testes and ovaries of young mice of AK line." *Acta Haemat*, 1953. **10**: 18-26.

80. Gross, L., "Neck tumors, or leukemia, developing in adult C3H mice following inoculation, in early infancy, with filtered (Berkefeld N), or centrifuged (144,000Xg), AK-leukemic extracts." *Cancer*, 1953. **6**: 948-957.

81. Gross, L., "Biological properties of the mouse leukemia agent." *Cancer*, 1953. **6**: 153-158.

82. Gross, L., "A filterable agent, recovered from AK leukemic extracts, causing salivary gland carcinomas in C3H mice." *Proc Soc Exper Biol and Med*, 1953. **83**: 414-421.

83. Gross, L., "The "vertical" transmission of mouse mammary carcinoma and chicken leukemia. Its possible implications for human pathology." *Cancer*, 1951. **4**: 626-633.

84. Gross, L., "Delayed effects of inoculation of AK-leukemic cells in mice of the C3H line. A working hypothesis on the etiology of mouse leukemia." *Cancer*, 1952. **5**: 620-624.

85. Interview with Ludwig Gross, M.D., October 28, 1992 at Dr. Gross's office at the Bronx VAMC.

86. Interview with Hyman Zimmerman, M.D., April 6, 1988 at Washington, DC VAMC.

87. Interview with Roger Egeberg, M.D., February 25 and 26, 1992 at Dr. Egeberg's home in Washington, DC.

88. Telephone interview with William Adams, M.D., February 17, 1992.

89. Telephone interview with William Valentine, M.D., February 14, 1992.

90. Coodley, E., Weiss, B. and Egeberg, R., "Reiter's Syndrome: Report of six cases." *Ann West Med Surg*, 1948. **2**: 500-505.

91. Egeberg, R., "Treatment of chest emergencies: medical aspects." *Ann West Med Surg*, 1951. **5**: 133-137.

92. Weir, R., Egeberg, R., Lack, A. and Leiby, G., "A clinical trial of prodigiosin in disseminated coccidioidomycosis." *Am J Med Sci*, 1952. **224**: 70-76.

93. Egeberg, R., "Coccidioidomycosis: its clinical and climatological aspects with remarks on treatment." *Am J Med Sci*, 1954. **227**: 268-271.

94. Telephone interview with Roger Egeberg, M.D., April 11, 1994.

95. Goldman, R., Asher, L. and Ware, E., "Hereditary hemorrhagic telangiectasis." *Gastroenterol*, 1949. **12**: 495-501.

96. Goldman, R., "The effect of aureomycin upon Hodgkin's Disease." *Am J Med Sci*, 1951. **221**: 195-198.

97. Lipsett, M. and Goldman, R., "Phenylbutazone toxicity: Report of a case of acute renal failure." *Ann Int Med*, 1954. **41**: 1075-1079.

98. Goldman, R., "Studies in diurnal variation of water and electrolyte excretion: Nocturnal diuresis of water and sodium in congestive cardiac failure and cirrhosis of the liver." *J Clin Invest*, 1951. **30**: 1191-1199.

99. Goldman, R. and Bassett, S., "Diurnal variation in the urinary excretion of neutral lipid-soluble reducing steroids in congestive heart failure and cirrhosis of the liver with ascites." *J Clin Invest*, 1952. **31**: 253-258.

100. Goldman, R., Adams, W. and Luchsinger, E., "Renal function in multiple myeloma." *J Lab Clin Med*, 1952. **40**: 519-522.

101. Goldman, R. and Bassett, S., "Effect of intravenous calcium gluconate upon the excretion of calcium and phosphorus in patients with idiopathic hypoparathyroidism." *J Clin Endocrinol Metab*, 1954. **14**: 278-286.

102. Goldman, R., "Creatinine excretion in renal failure." *Proc Soc Exper Biol and Med*, 1954. **85**: 446-448.

103. Blahd, W., Levy, M. and Bassett, S., "A case of Hand-Schuller-Christian Syndrome treated with cortisone." *Ann Int Med*, 1951. **35**: 927-937.

104. Leslie, A., Blahd, W. and Adams, W., "The effect of prolonged administration of epinephrine on adrenal cortical function and epinephrine tolerance in chronic asthmatics." *J Lab Clin Med*, 1953. **41**: 865-870.

105. Blahd, W. and Bassett, S., "Potassium deficiency in man." *Metabolism*, 1953. **2**: 218-224.

106. Adams, W., Leslie, A. and Levin, M., "The dermal loss of iron." *Proc Soc Exper Biol and Med*, 1950. **74**: 46-48.

107. Craddock, C., Adams, W. and Figueroa, W., "Interference with fibrin formation in multiple myeloma by an unusual protein found in blood and urine." *J Lab Clin Med*, 1953. **42**: 847-859.

108. Adams, W., Blahd, W. and Bassett, S., "A method of human plasmaphoresis." *Proc Soc Exper Biol and Med*, 1952. **80**: 377-379.

109. Adams, W., Mason, E. and Bassett, S., "Metabolic balance investigation of three cases of multiple myeloma during ACTH administration; Exchanges of calcium, phosphorus, nitrogen and electrolytes." *J Clin Invest*, 1954. **33**: 103-121.

110. Adams, W., Valentine, W., Bassett, S. and Lawrence, J., "The effect of cortisone and ACTH in leukemia." *J Lab Clin Med*, 1952. **39**: 570-581.

111. Levin, M., Fred, L. and Bassett, S., "Metabolic studies in gout." *J Clin Endocrinol Metab*, 1952. **12**: 506-518.

112. Levin, M., Rivo, J. and Bassett, S., "Metabolic studies in gout with emphasis on the role of electrolytes in acute gouty arthritis." *Am J Med*, 1953. **15**: 525-534.

113. Michael, M., Jr., Cole, R., Beeson, P. and Olson, B., "Sarcoidosis: Preliminary report on study of 350 cases with special reference to epidemiology." *Natl Tuberc Assoc*, 1950. **46**: 208-212.

114. Michael, M. and Whorton, C., "Delay of the early inflammatory response by cortisone." *Proc Soc Exper Biol and Med*, 1951. **76**: 754-756.

115. Bloom, W., Cummings, M. and Michael, M., "Macrophage content of oil-induced peritoneal exudate in rats and rabbits." *Proc Soc Exper Biol and Med*, 1950. **75**: 171-172.

116. Michael, M., Cummings, M. and Bloom, W., "Course of experimental tuberculosis in the albino rat as influenced by cortisone." *Proc Soc Exper Biol and Med*, 1950. **75**: 613-616.

117. Cummings, M., Hudgens, P., Whorton, M. and Sheldon, W., "The influence of cortisone and streptomycin on experimental tuberculosis in the albino rat." *Am Rev Tuberc*, 1952. **65**: 596-602.

118. Roche, P., Cummings, M. and Hudgens, P., "Comparison of experimental tuberculosis in cortisone-treated and alloxan-diabetic albino rats." *Am Rev Tuberc*, 1952. **65**: 603-611.

119. Sheldon, W., Cummings, M. and Evans, L., "Failure of ACTH or cortisone to suppress tuberculin skin reactions in tuberculous guinea pigs." *Proc Soc Exper Biol and Med*, 1950. **75**: 616-618.

120. Klein, G., Maltz, M., Cummings, M. and Fish, C., "Efficacy of centrifugation as a method of concentrating tubercle bacilli." *Am J Clin Path*, 1952. **22**: 581-585.

121. Lewis, G., Hankey, L., Adair, F. and Cummings, M., "A study of certain amino acids as they may relate to the problem of host resistance to tuberculosis." *Am Rev Tuberc*, 1952. **66**: 378-380.

122. Fleming, J., Runyon, E. and Cummings, M., "An evaluation of the hemagglutination test for tuberculosis." *Am J Med*, 1951. **10**: 704-710.

123. Cummings, M., "Diagnostic methods in tuberculosis. II. Demonstration of M. tuberculosis by culture." *Am J Clin Path*, 1951. **21**: 684-690.

124. Atkins, E. and Cummings, M., "Tuberculous meningitis: Treatment of spinal block with intrathecal administration of tuberculin." *New England J Med*, 1952. **247**: 715-717.

125. Cummings, M. and Livings, D., "The prevalence of streptomycin resistant tubercle bacilli among 5,526 patients admitted consecutively to hospitals." *Am Rev Tuberc*, 1954. **70**: 637-640.

126. Telephone interview with Richard Ebert, M.D., December 22, 1993.

127. Ebert, R., Borden, C., Wells, H. and Wilson, R., "Studies of the pulmonary circulation. I. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs in normal individuals." *J Clin Invest*, 1949. **28**: 1134-1137.

128. Borden, C., Ebert, R., Wilson, R. and Wells, H., "Studies of the pulmonary circulation. II. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs in patients with left ventricular failure." *J Clin Invest*, 1949. **28**: 1138-1143.

129. Borden, C., Ebert, R., Wilson, R. and Wells, H., "Pulmonary hypertension in heart disease." *New England J Med*, 1950. **242**: 529-534.

130. Borden, C., Wilson, R., Ebert, R. and Wells, H., "Pulmonary hypertension in chronic pulmonary emphysema." *Am J Med*, 1950. **8**: 701-709.

131. Borden, C., Ebert, R. and Wilson, R., "Anoxia in myocardial infarction and indications for oxygen therapy." *J Am Med Assn*, 1952. **148**: 1370-1371.

132. Wilson, R., Borden, C., Ebert, R. and Wells, H., "A comparison of the effect of voluntary hyperventilation in normal persons, patients with pulmonary emphysema, and patients with cardiac disease." *J Lab Clin Med*, 1950. **36**: 119-126.

133. Brown, C., Fry, D. and Ebert, R., "The mechanics of pulmonary ventilation in patients with heart disease." *Am J Med*, 1954. **17**: 438-446.

134. Stead, W., Fry, D. and Ebert, R., "The elastic properties of the lung in normal men and in patients with chronic pulmonary emphysema." *J Lab Clin Med*, 1952. **40**: 674-681.

135. Falk, A. and Ebert, R., "Tuberculous pericarditis treated with streptomycin." *J Am Med Assn*, 1951. **145**: 310-314.

136. Evans, R., Amatuzio, D. and Ebert, R., "Red blood cell studies: Ashby curves." *Science*, 1952. **115**: 572-573.

137. Schultz, A., Hammarsten, J., Heller, B. and Ebert, R., "A critical comparison of the T-1824 dye and iodinated albumin methods for plasma volume measurement." *J Clin Invest*, 1953. **32**: 107-112.

138. Hammarsten, J., Heller, B. and Ebert, R., "The effects of dextran in normovolemic and oligemic subjects." *J Clin Invest*, 1953. **32**: 340-344.

139. Falk, A., Zieve, L., Tucker, W. and Hanson, M., "The hepatic toxicity of amithiozone." *Am Rev Tuberc*, 1951. **64**: 159-169.

140. Heller, B., Jacobson, W. and Hammarsten, J., "The effect of cortisone in glomerulonephritis and the nephropathy of disseminated lupus erythematosis." *J Lab Clin Med*, 1951. **37**: 133-142.

141. Jacobson, W., Hammarsten, J. and Heller, B., "The effects of adrenaline upon renal function and electrolyte excretion." *J Clin Invest*, 1951. **30**: 1503-1506.

142. Tucker, W., "Evaluation of streptomycin regimens in the treatment of tuberculosis." *Am Rev Tuberc*, 1949. **60**: 715-754.

143. Borden, C., "Acute myocarditis. Report of a case with observations on the etiologic factor." *Am Heart J*, 1950. **39**: 131-135.

144. Borden, C. and Hall, W., "Fatal transfusion reactions from massive bacterial contamination of blood." *New England J Med*, 1951. **245**: 760-765.

(Intentionally Blank)

Chapter 4. Research Cooperation Between the NAS and VA

In 1945, as World War II drew to an end, Michael E. DeBakey, M.D., was a Colonel, the Chief of the Surgical Consultants Division of the Army's Surgeon General's Office. He recalled neurosurgeon Harvey Cushing's frustration at the lost opportunity to benefit from World War I medical experience with follow-up studies. DeBakey realized the important information to be gained from follow-up studies to learn the long-term outcome of war injuries and he worried that postwar interest in war-related medical research would wane.[1]

Figure 4.1: Michael DeBakey, M.D.

DeBakey wrote a memorandum to Surgeon General Kirk, recommending an NRC-coordinated joint effort of VA and the military services to mine military records and use follow-up studies to learn about medical outcomes.[2] At Kirk's request,[3] the NRC called a meeting of the Surgeons General of the Army, Navy and Public Health Service, the Medical Director of the Veterans Administration and the NRC. To outline a program, they formed an ad hoc committee that held two meetings in May and June of 1946 (Appendix IIc).

The group recommended that the Academy, through the National Resources Council (NRC) of the National Academy of Sciences, establish a standing Committee on Veterans Medical Problems. The NRC assigned Dr. DeBakey and Gilbert Beebe, Ph.D., a statistician who later became Chief of the Follow-up Agency, to write an action plan. Approved by the ad hoc committee, its recommendations included formation of a standing Committee on Veterans Medical Problems to advise the NRC and VA, and a Medical Follow-up Agency in the NRC to carry out studies of long-term outcomes of wartime injuries and illnesses.[4]

Committee on Veterans Medical Problems (CVMP)

The standing Committee on Veterans Medical Problems (Appendix IIc) first met on Sept. 20, 1946.[5] It became apparent that the originally proposed clinical follow-up research had to expand and include research by VA physicians. Chief Medical Director Hawley informed the CVMP that for a number of years the Veterans Administration would not be sufficiently staffed or equipped to

undertake research in major clinical and biological problems and could support only small clinical studies. Nevertheless, as early as the June 13, 1946, meeting of the planning committee,

> "Dr. (Perrin H.) Long called attention to the fact that investigative projects had already been planned or even set up, and that unless such work, costing a considerable amount of money, were supported, the younger men would not remain in the Veterans Administration."[6]

In fact, the intramural research program, research initiated by staff in VA hospitals (Chapter 3), took root simultaneously with the programs sponsored by the NAS through the CVMP.

The contractual relations between VA and the NRC that the CVMP reviewed fell into three categories:

1. VA contracts to non-VA institutions, primarily medical schools, for medical research. This program flourished through 1953, when it was almost entirely replaced by the VA intramural research program.
2. Prosthetics research contracts with academic and other non-VA institutions. The contract prosthetics research program continued until the late 1970s, when it was partially replaced by intramural VA rehabilitation research. Early on, the CVMP oversaw this program. Then, NRC advice began to come directly to VA from the NRC's Advisory Committee on Artificial Limbs (Chapter 20). The NRC role in reviewing prosthetics research contracts continued until 1976.
3. The Medical Follow-up Agency. In the early CVMP active period, the Follow-up Agency was funded entirely by VA. This Agency remained in the NRC until 1988 and then moved organizationally to the Institute of Medicine. With funding from multiple sources, the Follow-up Agency continues to play an active role in medical research.

The CVMP originally oversaw the entire VA research program, though this oversight role later decreased as the intramural program expanded. To complete the necessary scientific reviews, especially of contract requests, the NRC reestablished a system of advisory committees similar to the wartime NRC medical advisory committees.[7]

Those committees had begun to form in 1940, when the Surgeon General's Office of the Army asked the NAS for advice on chemotherapy and transfusions. At that time, the NRC formed two advisory committees of civilian specialists. Additional requests led to the creation of more committees, so that by June 1941, eight major medical committees and 33 subcommittees were active. With the onset of the war, the President's Office of Science and Technology (that sponsored, among other projects, work on the atomic bomb) became active and well funded. Its sponsorship of the medical research needed for the war effort was carried out by its Committee on Medical Research (CMR), which requested advice from these NRC committees. By 1943, 52 NRC committees and subcommittees, with 221 members, were advising the CMR, and most research contracts funded by the CMR were funded in response to an NRC committee's recommendation. To finance this committee structure, the Office of Science and Technology provided contractual support to NAS. The Chairman of the NAS Division of Medical Sciences became Vice Chairman of the CMR.

At the war's end, the CMR closed its contracts program. It, and the NRC committee structure supporting it, were abolished in 1946.[8] A postwar effort required a new start by the NRC, with new oversight and subject matter advisory groups.

By December 1946, the NRC had established advisory committees on medicine (with subcommittees on venereal diseases, cardiovascular diseases and tuberculosis), and on surgery, neuropsychiatry, chemotherapy, sanitary engineering, growth, prosthetic devices and sensory devices. The latter two committees and their successor committees were important to VA's early research in rehabilitation (Chapter 20).

CVMP's activity was funded by a separate VA contract to the National Academy of Sciences. It actively advised the VA research program, meeting 30 times from 1946 through 1953.

VA's extramural contracts program

Until the end of 1953, the CVMP reviewed all VA general research contracts, as well as follow-up studies. The Committee depended on reviews by NRC's subject matter committees, but the CVMP itself also reviewed all contract applications. In addition, it established a roster of consultant statisticians,[9] a concept unusual for the time.

During the first year, many contracts (Appendix IV) were for follow-up studies that required access to VA records or examination of VA patients. Prominent in those begun in 1947 was the follow-up study on peripheral nerve injuries, led by Barnes Woodhall, M.D., of Duke University. This study became part of the Follow-up Agency work and eventually resulted in a monograph.[10]

In 1948, VA-supported contracts included a spectrum of Veterans' medical care problems. One contract studied treatment of coccidioidomycosis, a problem among Veterans stationed in endemic areas. Even though new cases of syphilis were well treated with penicillin, tertiary syphilis continued to be a problem for VA patients, and in 1948 contracts were awarded for study of paresis and of cardiovascular syphilis. A contract with a Yale scientist explored the physiology of frontal lobotomy.

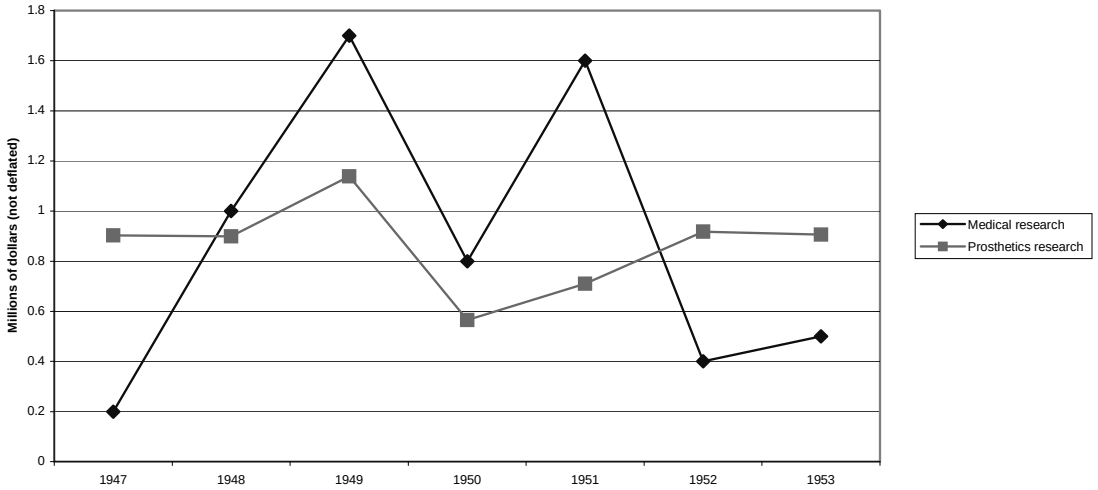
While many contract-supported investigators applied through their VA affiliates, most were medical school faculty members, and the medical schools administered the contracts. It is likely that some of this contract research was performed in the affiliated VA hospital. Contract recipients included such luminaries as Norman Brill, M.D., Barnes Woodhall, George Burch, M.D., Michael DeBakey, Harold G. Wolff, M.D., Thomas Sternberg, M.D., Paul Beeson, M.D., Milton Winternitz, M.D., George Taplin, M.D., I.L. Chaikoff, M.D., Ph.D., Brian Blades, M.D., Harold Beecher, M.D., Cyril N.H. Long, M.D., Franz Ingelfinger, M.D., Leslie Zieve, M.D., Ph. D, and Marshall Urist, M.D. University charges for overhead costs became a problem that Dr. Cushing discussed in a September 1951 report to VA's Special Medical Advisory Group:

> "One university . . . which proposed a contractual research project with the VA that was approved by the National Research Council has raised an issue on the overhead allowance proposed in the contract. The contract submitted by the VA to this university provided for twelve per cent of the total amount of the contract as overhead. The university came back and

said that they could not accept the contract as the overhead was entirely too low. The overhead which this school desired was either 44 per cent of the salaries and wages mentioned in the contract, or 31 per cent of the total amount of the contract. VA thanked them very much and said that the contract was not sufficiently important to it to proceed on that basis. . . . How far is 'Uncle Sugar' going to go in supporting, by overhead, some of these grants?"[11]

Administering these contracts burdened the very small VA Central Office research staff, and contracts were loosely supervised until Marjorie Wilson, M.D., joined the staff. Wilson recalled that she came to Washington, D.C., in 1951 and found a job in VA's Research and Education Service. When she arrived, she found three filing cabinets filled with 150-200 contracts that had not been organized in any way. She read all the contracts and systematized the files, establishing expense and result records and sending the progress reports to the NRC committees to help them in their annual reviews of renewal requests. VA contracts for prosthetics research (Chapter 18) were handled by the Prosthetics and Sensory Aids Service at that time.

Figure 4.2 VA expenditures for research contracts, 1947-1953



Dr. Wilson remembered the contract holders as the "giants" in academic medicine. Virtually all contracts were for clinical investigations.[12]

The Medical Follow-up Agency

The plan for follow-up studies devised by DeBakey and Beebe and debated by the 1946 ad hoc Committee on Veterans Medical Programs included a three-pronged approach:

1. A separate agency to be established to work with VA and armed services to perform follow-up studies on World War II Veterans;
2. A program of clinical follow-up research to be initiated by faculty of the affiliated schools on contract, and later included in an intramural research program; and
3. Large-scale epidemiologic studies.

At its first meeting in September 1946, the CVMP accepted the DeBakey-Beebe report and recommended that the NRC establish an independent Follow-up Agency, to be funded by a VA contract but administratively responsible to the NRC. The Medical Follow-up Agency was started, with Beebe as its statistical leader and John Ransmeier, M.D., as the medical leader. Over the next two years, Follow-up Agency staff worked closely with VA to put the follow-up program in motion.

Figure 4.3: Gilbert Beebe, Ph.D.

The Follow-up Agency's initial task was records identification. Some dedicated military physicians had developed personal rosters of Service personnel with conditions that especially interested them, and these were collected.[13] However, these records, by and large, were not usable for large-scale studies. It soon became apparent that it was necessary to find a way to work with the existing records systems. In March 1948, the Follow-up Agency reported to its organizational superior in the NAS that:

> "In December 1947 the Veterans Administration published Technical Bulletin 3-30, its 'Procedure for Following National Research Council Access to Information from Files of the Veterans Administration and Army Medical Records of World War II Veterans,' which made it possible to determine the present addresses of Veterans and to assemble their Army records in either Washington or an appropriate study center. In order to locate subjects for the various study centers, approximately 22,000 National Research Council Locator Requests have been processed through the Veterans Administration. Providing service medical records to the centers has necessitated calling in approximately 700 medical records from the Veterans Administration, exclusive of those obtained from the Army and Navy directly. This phase of the work is only beginning, the effort thus far having been confined to giving each study center an initial group of cases with which to test its procedures and make a start in its work. Cooperation from all portions of the far-flung Veterans Administration organization has been complete, but an endeavor of this scope inevitably proceeds slowly until there is wide understanding of just what is required."
>
> "The truly cooperative nature of the follow-up program is well illustrated by the full participation of both Army and Navy in the process of creating rosters and securing both

> personnel and medical records. Many tabulations have been made by the medical statistics divisions of both Army and Navy according to specifications established by the Committee, and listings and duplicate punch-cards have been furnished covering tens of thousands of admissions for many different conditions. Army personnel and medical records of World War II are housed in St. Louis, and it has been necessary to establish there a branch record office for the Committee in order to arrange necessary access to those records and to abstract or reproduce them as required by responsible investigators. Navy and Marine Corps records have been made available in similar fashion except that, until recently, they were concentrated in Washington, D.C. where personnel from the Committee's main record office could have access to them. The removal of non-current Navy records to Garden City will necessitate a small unit there unless the Navy can continue to call records back to Washington on request."[14]

Having Follow-up Agency staff work at the Armed Services' centralized records depots was successful, and good relations were maintained with the medical records departments of the Army and the Navy, as well as VA.[15]

An early problem in conducting follow-up studies was the VA General Counsel's decision that follow-up examinations performed for research purposes could not be combined with required medical examinations when a Veteran was applying for compensation. In those cases, the Veteran needed to make a separate trip, generally to a university clinic, for the follow-up examination, thus removing the financial motivation that encouraged the Veteran to cooperate in the compensation exam. To improve compliance in difficult cases, the Follow-up Agency worked with the Red Cross, which sent staff to intercede with the Veterans and help them get to the centers for examination.[15] This is described in the report of the study of peripheral nerve injuries:

> "At that point (when the man had not replied to repeated letters, including a certified letter) the center was considered to have exhausted its power of appeal and the man was referred to the American Red Cross, through its national headquarters, to help under a cooperative agreement worked out with the Follow-up Agency. Red Cross representatives were provided with a statement about the project and visited each center to learn something of the nature of the examination and of the essential medical interests of the investigators . . . . An immediate benefit of the Red Cross participation in the follow-up work was the information it provided about the apparent motivation of men who refused to participate and about the interaction between subjects and personnel of the follow-up center."[16]

Even before the Follow-up Agency became functional, proposals for studies poured in to the CVMP for review. As of December 1947, these included follow-ups of liver function following hepatitis, tuberculosis, schistosomiasis, peripheral nerve injuries, spinal cord injuries, aneurysms and fistulae, arterial injuries, psychoneuroses and epilepsy.[17] Some of these fell by the wayside, but a number became a part of the Follow-up Agency's long-term program.

By early 1949, the Follow-up Agency had planned a number of projects and pilot feasibility studies were under way.[18] At the same time, members of its statistical staff were increasingly called on for advice about other contracts under review by the CVMP. The Agency also assisted in planning and coordinating other VA contract follow-up studies at 30 centers, primarily universities. Most of these required actual reexamination of patients, rather than just records review. Seymour Jablon, a

mathematical statistician who joined the Agency in 1948, worked closely with Dr. Beebe and eventually replaced him as Chief when Beebe retired in 1977.[19]

Figure 4.4: Seymour Jablon

By late 1949, costs and the slow and uncertain return of results from follow-up studies were beginning to arouse the concern of the CMVP and the VA Research staff responsible for their funding. None of the studies had yet been published. Some of the contract follow-up studies were experiencing problems because they had been set up hastily. Faults in statistical design were surfacing. The CVMP ruled that any future proposals must be approved twice—once in concept and later, after input from the Follow-up Agency staff on the designs—before they were actually funded.[20]

In early 1951, VA and the CVMP jointly appointed a subcommittee to review the Follow-up Agency's activities. The Agency's cumulative cost through FY 1951 was $1.752 million. The subcommittee reported enthusiastically about the following projects under way, with comments on the status of results as of 1951:

> "Infectious Hepatitis. A follow-up of approximately 1,000 survivors of the original infection has revealed no residual of severe liver damage or evidence of progressive liver disease (Projects #22, #31, #49).
>
> Psychoneurosis. It is expected that the complete analysis will produce information of value to the Armed Forces in setting policies for induction, assignment to combat duty, and the disposition of men who break down in service (Project #7).

Peripheral Nerve Injuries. Emphasis is placed on the value of specialized neurologic treatment, use of special neuropsychological techniques as an adjunct to surgery, and improvement in the management of peripheral nerve injuries (Project #13).

Arterial Injuries. The study has developed methods for objective study and information concerning improved handling of vascular injuries (Projects #14-17).

Schizophrenia. The average length of service prior to breakdown was two and a half years. The majority could have been detected by adequate study at time of induction (Project #18).

Tuberculosis. The incidence of more than 25% of positive tuberculin reactors among Veterans is almost double that of non-Veterans. The incidence of positive reactors increases with the length of service (Project #20). The final analysis should develop data on which constructive recommendations may be made to the Armed Forces for improved screening procedures for tuberculosis at admission and discharge (Project #89).

Tumors of the Testis. The result of this study of the largest known series of testicular tumors (approximately 1,000) indicates significant differences in the prognosis for certain types. Pure seminomas (comprising about 40% of this total) had a five-year mortality rate of 1%; other types and combinations had 5-year mortalities ranging from 40 to 75%.

Rheumatic Fever. The conclusions resulting from the final analysis should reveal significant information concerning future induction of men with history of rheumatic fever and the disposition of men having this disease while in service (Project #65).

Million-volt Irradiation. Among the late effects of million-volt irradiation are fibrosis of the lung, and severe damage to the gastrointestinal tract including ulceration, perforation and obstruction. Any dose above 2,000r may produce severe tissue damage; however some patients are able to withstand 4,000r. ”

All of these were studies of World War II Veterans, aimed at discovering the long-term effects of diseases and injuries incident to their service. By their very nature, these studies required time to accumulate data, but by this time the reviewers wanted to see at least intermediate results. Most of the studies in this list did have outcomes published shortly after this report. Results of the hepatitis studies have stood the test of time.[21] The psychoneurosis studies formed the basis for adjusting psychiatric standards for mobilization.[22] The irradiation studies led to methods of evaluating tolerance levels for the gastrointestinal tract.[23]

After reviewing this report, the CVMP enthusiastically endorsed the Follow-up Agency's activities.[24]

Figure 4.5. Meeting, about 1950, of the group working on the follow-up study of WWII vascular injuries. Dr. Beebe is second from left, second row, and Dr. DeBakey is at the far right, front row.

A year later, however, some concern remained about the effectiveness of the Follow-up Agency. Dr. Milton Winternitz, Chairman of the NAS Division of Medical Sciences, commented to the CVMP that the total cost over five years, including all follow-up activities, had been $2.4 million, with "relatively little harvest to date." None of the major projects had yet been completed. The CVMP again appointed an ad hoc committee to review the status of the follow-up studies.[25] This led to an in-depth review by Donald Mainland, Ph.D., Professor of Medical Statistics at New York University. In his report of March 22, 1953, Mainland praised the statistical excellence of the Follow-up Agency staff but pointed to problems caused by early enthusiasm, large numbers of hastily planned studies, and more recent lagging because of clinician investigators' competing responsibilities. He advised NRC to phase down the program and use its statistical staff to improve the quality of NRC-sponsored research.[26]

By 1953, of 26 follow-up studies, eight were completed, 14 were targeted for completion over the next 18 months, two had been abandoned, and two long-term studies had no projected completion date. The NRC and VA placed a moratorium on starting new follow-up studies.[27]

Until 1954, VA provided all support for the Follow-up Agency. During late 1953, VA found it necessary to reduce the Follow-up Agency annual budget abruptly from $228,000 to $163,000. The

Agency had to drop 10 staff members. Dr. R. Keith Cannan, Sc.D. described the situation to a meeting of the Executive Committee of the NRC Division of Medical Sciences:

> "The future of the Follow-up Agency of the Division is in jeopardy. The Veterans Administration's 1954 budget request has been cut from 6.5 to 5.5 million dollars, while the number of their research laboratories has approximately tripled in three years. At the same time, there has been a shift in emphasis from extra-mural to intra-mural research. The question now before the Division is whether or not an effort should be made to maintain the Follow-up Agency."

After extensive discussion, the committee resolved that:

> "The medical experience of the Armed Forces and of the Veteran population provide a unique opportunity for medical follow-up studies of importance to clinical medicine and to the Armed Forces and the Veterans Administration. The Division of Medical Sciences provides a logical focus of leadership and organization for the many interests in such studies, and steps should be taken to re-establish, as a broad inter-agency program, a significant program of follow-up studies."[20]

The Follow-up Agency prepared a new plan, eventually adopted, in which they would seek support from VA and other agencies as well. They would keep a small "core" staff, which would be temporarily enlarged when new projects were funded. VA support would come as a contribution to "core" and also to specific contracts.[28]

By the end of 1954, the Follow-up Agency was still on shaky ground and continued to seek a stable funding base. By this time, only four of its original 26 projects were still current. Owing to the moratorium, no new projects had been added.[29]

Within a few months the situation improved: three projects continued under VA sponsorship, but now the Army and the U.S. Public Health Service were each sponsoring two new projects.[30] Multiple-agency funding continued thereafter.

Studies in Several Key Areas

In 1954, the Follow-up Agency, working with VA neurologist John Kurtzke, M.D., undertook its first controlled clinical trial. This study resulted from the observation that isoniazid, given to a patient with both tuberculosis and multiple sclerosis, appeared to lead to improvement in his multiple sclerosis. After the initial serendipitous observation, 30 patients with multiple sclerosis were treated with isoniazid and "ninety percent . . . showed striking improvement over a period of two years in comparison with controls from an earlier period."[31] With the encouragement of the CVMP, the Follow-up Agency coordinated a study of 186 multiple sclerosis patients in 11 VA hospitals, comparing 100 mg isoniazid thrice daily with placebo. The results were negative: "By all criteria, including laboratory findings and over-all clinical impressions, the differences between the isoniazid and placebo groups were insignificant. No beneficial effects that could be ascribed to isoniazid in multiple sclerosis were observed in nine months or more of follow-up."[32] In this, one of the earliest placebo-controlled clinical trials, this particular treatment was laid to rest. However,

the collaborating group built on this study to conduct a five-year follow-up of the clinical course of these well-studied patients with this puzzling disease.[33] There were 52 deaths during the five-year period. Eight patients improved, 35 were unchanged, and in the others, the disease worsened. Mortality was directly related to severity of the disease at the time of the original study. There was no long-term difference between patients treated with isoniazid during the controlled trial and those given placebo.

When, in 1957, VA began collaborative studies with the National Cancer Institute on the value of adjunctive chemotherapy in surgical oncology (Chapter 13), the Follow-up Agency broadened its support of the VA research program by providing ongoing statistical support.

The leaders of the Follow-up Agency recognized early on the value of follow-up studies in pairs of twins. From the mid-1950s, they explored the possibility of establishing a twin registry. In 1958, partially funded by VA, the Agency staff began the long, complex process of assembling a roster of Veteran twin pairs from World War II. They started with lists of male twins born between 1917 and 1927 in 29 states. Of the 45,000 male twin pairs identified, there were 8,000 where both were Veterans. To determine zygosity (whether identical or fraternal) of these twin pairs, the Follow-up Agency asked the FBI for copies of their fingerprints that were made at induction into the military. The FBI found this to be difficult and provided only some of the fingerprints. In addition, all subjects answered a questionnaire that included the question "As children, were you and your twin as alike as two peas in a pod?" The answer to this question correlated 95 percent with the results of fingerprint matching, and it was used to classify zygosity when fingerprints were not available.

A special committee reviewed all requests to use the twin registry and used strict criteria in their review, turning down two of the first three requests. The concern was to avoid unduly troubling the subjects while maintaining the registry by contacting them periodically. Some studies conducted in subsequent years required the twins to appear for examination, but most depended on records. Altogether, some 200 articles have been published that used this twin registry as a resource.

The Follow-up Agency later assisted VA in setting up a registry of Vietnam-era Veteran twins; this is now managed as a part of VA's intramural epidemiologic program.[34]

Results of Follow-up Agency studies

All told, between 1949 and 1996, the Follow-up Agency played a key role in studies leading to some 500 publications.[35] Its bibliography has been described as "a chronicle of the history of epidemiology in military and Veteran populations."[36]

Among the results of the early VA-sponsored Follow-up Agency studies were:

Infectious hepatitis. A group of 367 men living in the Minneapolis area who had documented hepatitis during World War II, including 69 with multiple attacks, received thorough workups four to six years later. They were compared with 137 men who had been heavily exposed to hepatitis without a clinical episode and to 212 controls. There were no significant differences among the groups.[21] A separate study from Philadelphia showed similar results in 271 men who had suffered clinical hepatitis, 138 "heavily exposed" men and 242 controls.[37] A third study was a 10-year follow-up of 460 men with acute hepatitis who were subjects of controlled treatment trials during

the Korean War. At follow-up, there was no difference between groups treated in different ways (bed rest, forced diet).[38]

Psychoneurosis. The psychiatric status of 955 former enlisted personnel diagnosed with psychoneurosis during their service was studied about five years after the original episode. Only 11 percent of these Veterans had sought psychiatric care from VA. Of the total, 62 percent came in for examination by a psychiatrist and information about all but 1.5 percent was available from some source such as VA records. The mortality pattern in the sample matched that of the general population except for an increase in suicides (six compared with an expected two). Only 1.8 percent were judged to be psychotic at follow-up, but 72 percent were judged to have some psychiatric disease. In general, the trend was judged to be toward improvement over time.[39, 40]

Peripheral nerve injury. In this study, one of the first approved by the CVMP, late results in 3,656 World War II peripheral nerve injuries were assessed in five clinical centers. The study supported use of radical surgery for complete loss of nerve function but conservative treatment when nerve continuity has not been interrupted. It also demonstrated the value of physical therapy in recovery of function. The study showed an inverse relation between functional recovery and the distance from the lesion to its area of principal innervation.[41]

Tuberculosis. This study compared induction and discharge chest x-rays of about 3,000 men discharged from the military for tuberculosis and 3,000 matched controls. In about half of those discharged for tuberculosis, evidence of tuberculosis was present in the induction film. New tuberculosis was more frequent in non-whites; in tall, thin men; and in former prisoners of war.[42]

Rheumatic fever. 135 randomly selected men with confirming records of diagnosis were examined three to eight years after Army hospitalization for acute rheumatic fever. At the follow-up examination, 32 of these men (23.7 percent) had rheumatic heart disease, a lower incidence than seen after rheumatic fever in children. Even in those with physical evidence of rheumatic heart disease, most were living normal lives with 95 percent employed or in school.[43]

Sarcoidosis. This was an epidemiological study of the 350 cases of sarcoidosis recognized among Armed Forces personnel during World War II. Residence in rural areas of the Southeast within regions of fine sandy soil appeared to favor development of sarcoidosis, and it was seen more frequently in blacks.[44, 45]

Hand injury. Follow-up of 104 patients with severe war wounds to the hand showed that adequate physical therapy is of great importance to functional recovery, and more important than reconstructive surgery that might require immobilization of the hand. All but four of the men studied were employed at follow-up.[46]

Combat-related schizophrenia. Two physicians who had treated 341 patients with acute schizophrenia in New Guinea during World War II were able to make personal contact with 156 of them five to eight years after the initial episode. They followed the remainder through VA records. Thirty control subjects, selected by the Follow-up Agency, were also examined. Although there was a trend toward improvement with time, 186 of the patients were still considered moderately or severely impaired five or more years after the initial episode. Neither the military nor the domestic

experiences of the schizophrenic patients differed from controls. The authors concluded that there is little profit to be gained in attempting to screen out those who may have schizophrenia at induction.[47, 48]

Prisoners of War. The Follow-up Agency has carried out a series of studies of long-term morbidity and mortality of former prisoners of war (POWs). The first, published in 1955, showed that overall mortality was increased in World War II POWs from the Pacific, but not the European, theater. This excess mortality was almost entirely due to tuberculosis and accidents.[49] In the second study, which included Korean War Veterans, POWs also had excess mortality.[50] However, by 1975 this excess in mortality rate had waned in both World War II and Korean War ex-POWs.[51] A 1975 study of morbidity in former POWs showed the most frequent illnesses to be psychiatric, with higher rates of hospitalization and VA disability. Excess morbidity correlated well with retrospective accounts of captivity weight loss, nutritional deficiencies and other associated symptoms.[52]

Head injuries. This was a follow-up of 739 World War II Veterans who had suffered penetrating wounds of the brain. Four centers examined their status extensively some 10 years after their injuries. Epilepsy, found in 28 percent, was worse and more frequent when the wounds were larger and deeper. Impaired judgment and altered personality were also related to the size of the wound, but not to its location.[53, 54]

Buerger's disease. Epidemiology and 10-year prognosis were studied in 936 Army males with Buerger's Disease documented from 1942 to 1948. Compared with Army men in general, those with the disease were older, more likely to be officers and more likely to be Jews. Incidence was estimated at about 3.5 per 100,000 Army men aged 20-44. Mortality was increased and related to severity of the disease. Amputations and sympathectomies also were related to disease severity at onset, and neither decreased in frequency with time.[55]

Hodgkin's disease. Epidemiology of, and survival over 17 years from, Hodgkin's Disease were studied in 388 documented cases, diagnosed during World War II. Patients with Hodgkin's Disease were better educated, of higher economic class and less likely to be married than Army men in general. The number of signs and symptoms of the disease at onset correlated with the histologic type and with survival. After 17 years, 8.4 percent of the men with granuloma and 28.6 percent of those with paragranuloma were alive. All five men with Hodgkin's sarcoma died within one year.[56]

Ulcerative colitis. In a study of the epidemiology of ulcerative colitis among Army men in 1944, 525 patients were compared with matched controls. The incidence was seen to rise with age, and Jews were affected more than twice as frequently as non-Jews.[57] In a follow-up study of mortality from these samples, 10.7 percent of the patients with ulcerative colitis died in the first 17 years after the index hospitalization, compared to 5 percent in the controls. Half of this excess mortality was due to ulcerative colitis, generally within the early years after diagnosis. The other half was due to cancer of the colon, most frequently in later years. A bad prognosis correlated strongly with the extent of colon involvement in X-rays made in 1944.[58]

Missiles in the heart. Forty men who survived missiles in the heart which had not been removed were studied 17 to 20 years after their injuries. Most had normal electrocardiograms and chest X-

rays at follow-up. Pericarditis had occurred in 25 percent. Only one patient had had serious migration of the missile. However, all of those examined suffered a "formidable strain of living with a missile in the heart," and five were totally incapacitated by an anxiety neurosis.[59]

Lumbar disk disease. The epidemiology of herniated nucleus pulposis (HNP) was studied in 1,095 first Army admissions, matched on age and period of World War II service with holders of Army National Life Insurance policies. HNP was found to be associated with mechanical factors related to body build (excess height, excess weight, good posture) and occupation (enlisted, ground combat, craftsman, rural residence). There was no difference from controls in prior service hospitalizations, including those for trauma.[60]

There has been speculation that it might have been better if the Follow-up Agency had originally been made a part of VA.[19] Among the reasons cited was that such an arrangement would have given needed stability, though it might have reduced the Agency's freedom of action. Also, participation in a strong in-house VA biostatistics and epidemiology program in the early days could have enriched the VA program and provided guidance and consistency. Feedback from VA could have improved the early follow-up studies.

On the other hand, as an independent agency, the Follow-up Agency was able to branch out to other sources of funding when VA's attention turned toward other priorities. It could meet urgent non-VA needs, such as those of the Atomic Bomb Casualties Commission. And though the Agency grew away from its VA roots, relations between the Follow-up Agency and VA Research remained good through the years and continue to be mutually beneficial.

Closing of the Committee on Veterans Medical Problems

By 1954, CVMP activity was winding down. The Follow-up Agency was well established. As the VA intramural program reached firmer ground, the research program had turned away from supporting research contracts.[61] Review of the contracts program, a key role of the CVMP, was no longer necessary. The CVMP no longer oversaw the prosthetics research program. From 1954 to 1959, the CVMP met only about once a year to review the overall VA research program and oversee the Follow-up Agency. It formally disbanded at the end of 1962.[62]

References

1. Letter from Gilbert W. Beebe, P.D. to author, written at Bethesda, MD, July 5, 2002.

2. Letter from Michael DeBakey, M.D. to Norman T. Kirk, Surgeon General of the Army, written at the Pentagon, March 5, 1946.

3. Letter from Norman T. Kirk to Frank B. Jewitt, President of the National Academy of Sciences, written at Washington, D.C.,

4. National Research Council, *Report on the Value and Feasibility of a Long-Term Program of Follow-up Study and Clinical Research.* Washington, D.C.: National Academy of Sciences, 1946.

5. National Academy of Sciences - National Research Council. "Minutes of First Meeting, Committee on Veterans Medical Problems." September 20, 1946. Washington, D.C.: National Research Council,

6. National Research Council, *Report on Follow-up Study and Clinical Research.*

7. National Academy of Sciences - National Research Council. "Minutes, Second Meeting of the CVMP." December 9, 1946. Washington, D.C.: National Research Council.

8. Richards, A.N., "Foreword," in *Advances in Military Medicine Made by American Investigators Working under the Sponsorship of the Committee on Medical Research*, Andrus, E.C., Bronk, D.W., Carden, G.A., Keefer, C.S., Lockwood, J.S., Wearn, J.T., and Winternitz, M.C., Editors. 1948, Little, Brown and Company: Boston.

9. NAS-NRC. "Minutes, First Meeting of the CVMP." September 20, 1946, 29.

10. *Peripheral Nerve Regeneration: A Follow-up Study of 3,656 World War II Injuries*. Woodhall, B. and Beebe, G.W., eds.; Washington, D.C.: U.S. Government Printing Office, 1957.

11. Cushing, E.H. "Minutes, Special Medical Advisory Group." Washington, D.C., 9.

12. Interview with Marjorie T. Wilson, M.D., April 29, 1988 at Dr. Wilson's office at ECFMG, in Washington, D.C.

13. National Academy of Sciences - National Research Council. "Minutes, Third Meeting of the CVMP." March 14, 1947. Washington, D.C.: National Research Council, Appendix C.

14. Medical Follow-up Agency "Report to Chairman, Division of Medical Sciences, National Academy of Sciences." 1948. 3-4.

15. Interview with Gilbert W. Beebe, Ph.D. and Seymour Jablon, May 3, 1988 at Mr. Jablon's office at NIH.

16. *Peripheral Nerve Regeneration*. Woodhall and Beebe, eds.; 1957, 18-19.

17. National Academy of Sciences - National Research Council. "Minutes, Fifth Meeting of the CVMP." December 11, 1947. Washington, D.C.: National Research Council.

18. Medical Follow-up Agency "Report to Chairman, Division of Medical Sciences, National Academy of Sciences." 1949. 5.

19. Interview with Gilbert W. Beebe, Ph.D., June 1, 1994 at a hotel lobby in Washington, DC.

20. National Academy of Sciences - National Research Council. "Minutes, Fourteenth Meeting of the CVMP." November 18-19, 1949. Washington, D.C.: National Research Council.

21. Zieve, L., Hill, E., Nesbitt, S. and Zieve, B., "The Incidence of Residuals of Viral Hepatitis." *Gastroenterology*, 1953. **25**: 495-531.

22. Brill, N.Q. and Beebe, G., "Some Applications of a Follow-up Study to Psychiatric Standards for Mobilization." *Am J Psychiatry*, 1952. **109**: 401-420.

23. Amory, H. and Brick, I., "Irradiation Damage of the Intestines Following 1000-Kv Roentgen Therapy." *Radiology*, 1951. **56**: 49-57.

24. Medical Follow-up Agency "Report to Chairman, Division of Medical Sciences, National Academy of Sciences." 1951. 5.

25. National Academy of Sciences - National Research Council. "Minutes, Twenty Fifth Meeting of the CVMP." December 5, 1952. Washington, D.C.: National Research Council.

26. Mainland, D. "The VA-NRC Program of Follow-up Studies: Evaluation and Suggestions." 1953.

27. Follow-up Agency "Report, Division of Medical Sciences, NRC." 1953.

28. National Academy of Sciences - National Research Council. "Minutes, Twenty Eighth Meeting of the CVMP." December 7, 1953. Washington, D.C.: National Research Council.

29. National Academy of Sciences - National Research Council. "Minutes, Thirtieth Meeting of the CVMP." Washington, D.C.: National Research Council.

30. National Academy of Sciences - National Research Council. "Minutes, Thirty First Meeting of the CVMP." April 15, 1955. Washington, D.C.: National Research Council.

31. NAS-NRC. "Minutes, Thirtieth Meeting of the CVMP." November 2, 1954. Washington, D.C.: National Research Council.

32. Veterans Administration Multiple Sclerosis Study Group, "Isoniazid in treatment of multiple sclerosis: Report on Veterans Administration Cooperative Study." *JAMA*, 1957. **163**: 168-172.

33. Veterans Administration Multiple Sclerosis Study Group, "Five year follow-up on multiple sclerosis: Report on Veterans Administration Cooperative Study." *Archives of Neurology*, 1964. **11**: 583-592.

34. Berkowitz, E.D. and Santangelo, M.J., *The Medical Follow-up Agency: The First Fifty Years, 1946-1996*. Washington, D.C.: National Academy Press, 1999, 27-28, 31, 45, 65, 67.

35. Berkowitz and Santangelo, *Medical Follow-up Agency*. 87-124.

36. Remington, R. "Remarks by Chairman, Committee on Epidemiology and Veteran Follow-up Studies, Commission on Life Sciences, National Research Council." *Conference on Epidemiology in Military and Veteran Populations*, quoted in Report of an Ad Hoc Executive Committee charged to review the Medical Follow-up Agency, July 27, 1987.

37. Neefe, J., Gambescia, J., Kurtz, C., Smith, H., Beebe, G., Jablon, S., Reinhold, J. and Williams, S., "Prevalence and nature of hepatic disturbance following acute viral hepatitis with jaundice." *Ann Intern Med*, 1955. **43**: 1-32.

38. Nefzger, M. and Chalmers, T., "The treatment of acute infectious hepatitis." *Am J Med*, 1963. **35**: 299-309.

39. Brill, N.Q. and Beebe, G., "Follow-up study of psychoneuroses." *Am J Psychiatry*, 1951. **108**: 417-425.

40. Brill, N.Q. and Beebe, G.W., *A Follow-up Study of War Neuroses*. VA Medical Monograph. Washington, D.C.: U.S. Government Printing Office, 1955.

41. *Peripheral Nerve Regeneration*. Woodhall and Beebe, eds.; 1957.

42. Long, E.R. and Jablon, S., *Tuberculosis in the Army of the United States in World War II*. VA Medical Monograph. Washington, D.C.: U.S. Government Printing Office, 1955.

43. Engleman, E.P., Hollister, L.E. and Kolb, F.O., "Sequelae of rheumatic fever in men. Four to eight year follow-up study." *JAMA*, 1954. **155**: 1134-1140.

44. Michael, M., Jr., Cole, R., Beeson, P. and Olson, B., "Sarcoidosis: Preliminary report on study of 350 cases with special reference to epidemiology." *Natl Tuberc Assoc*, 1950. **46**: 208-212.

45. Gentry, J.T., Notowsky, H.M. and Michael, M., "Studies on the epidemiology of sarcoidosis in the United States: The relationship to soil areas and to urban-rural residence." *J Clin Invest*, 1955. **34**: 1839-1856.

46. Freni, D.R. and Warren, R., "End-results of rehabilitation of war wounds of the hand." *Arch Surg*, 1951. **63**: 774-782.

47. Ripley, H. and Wolf, S., "Long-term study of combat area schizophrenic reactions." *Am J Psychiatry*, 1951. **108**: 409-416.

48. Ripley, H. and Wolf, S., "The course of wartime schizophrenia compared with a control group." *J Nerv Ment Dis*, 1954. **120**: 184-195.

49. Cohen, M.B. and Cooper, M.Z., *A Follow-up Study of World War II Prisoners of War*. VA Medical Monograph. Washington, D.C.: U.S. Government Printing Office, 1955.

50. Nefzger, M., "Follow-up studies of World War II and Korean War prisoners." *Am J Epidemiology*, 1970. **91**: 123-138.

51. Keehn, R.J., "Follow-up studies of World War II and Korean Conflict prisoners: III. Mortality to January 1, 1976." *Am J Epidemiology*, 1980. **111**: 194-211.

52. Beebe, G.W., "Follow-up studies of World War II and Korean War prisoners. II. Morbidity, disability, and maladjustments." *Am J Epidemiology*, 1975. **101**: 400-422.

53. Walker, A. and Jablon, S., "A Follow-up of head-injured men of World War II." *J Neurosurg*, 1959. **16**: 600-610.

54. Walker, A.E. and Jablon, S., *A Follow-up Study of Head Wounds in World War II*. VA Medical Monograph. Vol. 16. Washington, D.C.: U.S. Government Printing Office, 1961, 600-610.

55. De Bakey, M.E. and Cohen, B.M., *Buerger's Disease: A Follow-up Study of World War II Army Cases*. Springfield, IL: Charles C. Thomas, 1963

56. Cohen, B.M., Smetana, H.F. and Miller, R.W., "Hodgkin's Disease: Long survival in a study of 388 World War II Army Cases." *Cancer*, 1964. **17**: 856-866.

57. Acheson, E.D. and Nefzger, M.D., "Ulcerative colitis in the United States Army in 1944. Epidemiology: Comparisons between patients and controls." *Gastroenterology*, 1963. **44**: 7-19.

58. Nefzger, M. and Acheson, E., "Ulcerative colitis in the United States Army in 1944. Follow-up with particular reference to mortality in cases and controls." *Gut*, 1963. **4**: 183-192.

59. Bland, E. and Beebe, G., "Missiles in the heart. A twenty-year follow-up report of World War II cases." *New Eng J Med*, 1966. **274**: 1039-1046.

60. Hrubek, Z. and Nashold, B.S., "Epidemiology of lumber disk lesions in the military in World War II." *Am J Epidemiology*, 1975. **102**: 366-376.

61. National Academy of Sciences - National Research Council. "Minutes, Twenty Ninth Meeting of the CVMP." Washington, D.C.: National Research Council, 5.

62. Letter from R. Keith Cannon to members of the Committee on Veterans' Medical Problems, written at Washington, D.C., September 19, 1962.

(Intentionally Blank)

Chapter 5. The Tuberculosis Treatment Trials

Tuberculosis was a major public health problem in the 19th century and first half of the 20th century. Thanks in part to public health action, especially isolation of active cases and the campaign against public spitting, the incidence of the disease generally decreased in the United States. Deaths from tuberculosis declined from 195 per year per 100,000 population in 1900, to 113 in 1920 and 46 in 1940.[1] However, military personnel during wartime were exposed to crowding, disease and poor nutrition. Many who served in the two World Wars contracted tuberculosis.

Tuberculosis in the World War I Veteran

In 1917, when the United States was on the brink of World War I, a new law defining the nation's responsibility to provide for the health of those who served in its wars replaced the previously politically driven pensions system (Chapter 1). Under this new law, injured and ill former servicemen had the right to care in government hospitals.[2]

Patients with tuberculosis were prominent among those needing care in Veterans' hospitals, and accounted for 12 percent of the 178,000 World War I service disability discharges.[3] During the early and mid-1920s, a network of Veterans' hospitals devoted entirely to the care of the tuberculous grew up in the United States.

Before the Veterans' Bureau was established, World War I Veterans stricken with tuberculosis were treated in U. S. Public Health Service hospitals, but the number of beds was inadequate and allowed care of only a small minority. Many World War I Veterans stricken with tuberculosis were hospitalized in private hospitals under government contract. Many others stayed home, where they often infected their families and friends. New VA tuberculosis beds were filled as soon as they became available. The number of hospitalized Veterans with tuberculosis skyrocketed from 12,000 in 1920 to a 1922 peak of 44,951.[3] After that, the number of Veterans' tuberculosis admissions decreased and stabilized at about 11,000 per year from 1929 through 1945.[4]

In this pre-antibiotic era, VA care for tuberculosis was considered to be the best in the nation. Following the advice of the American Tuberculosis Association,[5] hospitals were placed in locations considered best for controlling the disease. These were in areas away from cities, often in the mountains, where the clear air was thought to be beneficial. Even though a 1927 Veterans' Bureau study showed that climate had no effect on outcome of tuberculosis,[6] the generally held medical opinion was that it did. Patients were kept in bed because bed rest was the mainstay of treatment. Increasingly, pneumothorax and thoracoplasty, operations to rest the diseased area of lung, became accepted treatment for tuberculosis and were added to bed rest.[7, 8]

The Medical Council, VA's advisory council in the 1920s and 1930s (Chapter 1), included a special group to consider treatment of tuberculosis. They advised on such matters as frequency of refills of pneumothorax, evaluation of "arrested" cases needing readmission and frequency of bacteriological studies.[9]

In 1926, VA's new Research Subdivision's published its first report: a statistical analysis of Veterans hospitalized with tuberculosis who also had a second disability. Nearly 39,000 such

Veterans had been hospitalized since 1919.[10] Significantly more Veterans with far advanced tuberculosis and a second disability were "colored" (62 percent) than white (42 percent). The following year, a systematic study of Veterans examined the prevalent view that climate influences the outcome of tuberculosis treatment.[6] Treatment results at the 19 Veterans' tuberculosis hospitals scattered throughout the country in a variety of climates and settings were correlated with their climatic conditions. The study concluded that "climate is not an important factor, and does not influence the end results."

During the period between the two World Wars, tuberculosis remained one of the most important problems of Veterans' medical care, though the fraction of tuberculous patients in Veterans' hospitals declined from 40 percent in 1922 to 8 percent in 1941.[11, 12] VA's own medical journal, the *Medical Bulletin*, published articles by VA staff that generally reflected their thoughts about their attempts to improve patients' care. In the year 1927 alone, the *Medical Bulletin* published 10 clinical research articles about tuberculosis. Topics included treatment of bone tuberculosis by actinotherapy,[13] heliotherapy in laryngeal tuberculosis,[14] statistical analysis of tuberculosis in mental hospitals,[15] interaction between tuberculosis and intercurrent diseases,[16] an outcomes study of 500 cases of pulmonary tuberculosis,[17] a systematic (negative) study of the effect of climate on outcome of tuberculosis treatment[6] and an essay on the history of tuberculosis.[18] There were case reports of lupus vulgaris,[19] generalized tuberculous adenitis,[20] tuberculous pericarditis[21] and tuberculous duodenal ulcer.[22] Also published were various essays on the importance of early diagnosis of tuberculosis,[23] proper history taking[24] and advice about care of the tuberculous patient.[25]

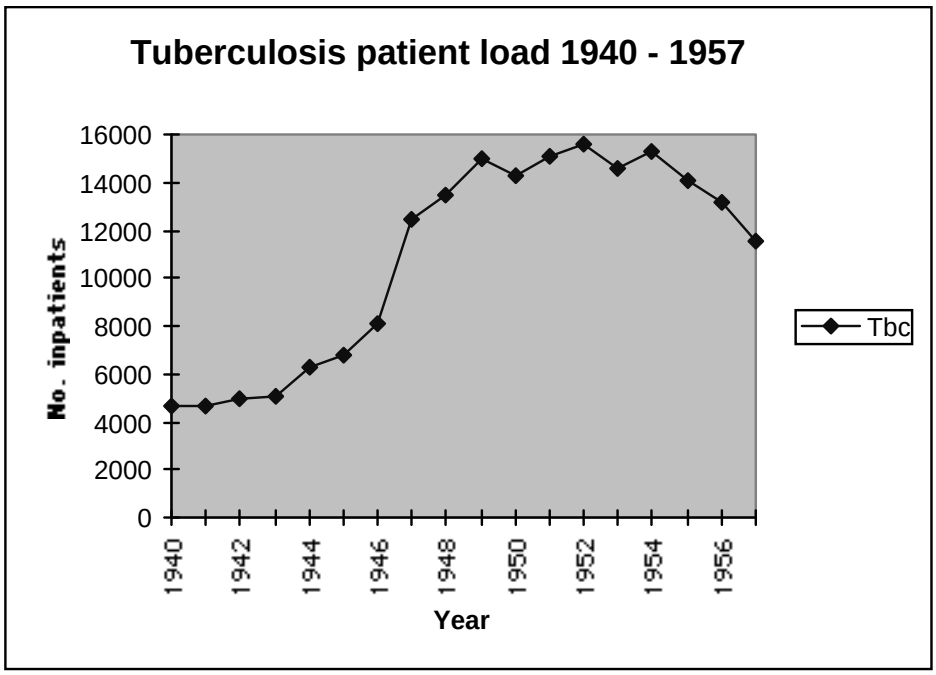


Figure 5.1. Number of patients with tuberculosis in VA hospitals, 1940-1957

Tuberculosis in the World War II Veteran

As the United States mobilized for the Second World War, the Veterans Administration staff dwindled.[26] Doctors and nurses were needed in the military. When they left VA, there were no replacements. Facilities deteriorated because of shortage of staff and materials for upkeep. At the end of the war, the sudden influx of demobilized soldiers, many with tuberculosis, created overcrowding and short staffing. In some cases, patient care was not good and the patriotic public was alerted through newspapers and magazines.[27] Eleanor Roosevelt learned of the situation and informed President Truman.[28] It was at that point that Truman called on General Omar Bradley to head VA., with Bradley, in turn, naming General Paul Hawley to head VA's medical department.

One of the first problems Hawley tackled was the needs of the new Veterans who had tuberculosis. At that time, some 12,000 Veterans were hospitalized in VA hospitals for tuberculosis, and their number was growing steadily.

Hawley persuaded John Barnwell, M.D., a professor at the University of Michigan, to come to Washington to lead the VA fight against tuberculosis. Barnwell was a well-known authority on the disease, who himself had been treated for tuberculosis. Equally important, he was active in the American Trudeau Society (a non-government organization advocating tuberculosis research) and a personal friend of leaders in the field. His goal was to use every resource available to him to improve the care of the tuberculous Veteran.

Figure 5.2. John Barnwell, M.D.

In 1946, the best medical centers and sanitoria continued to treat tuberculosis with rest therapy. Patients were confined to special hospitals or to special units in general hospitals. Complete bed rest was enforced, with patients not even getting up to use the bathroom. Pneumothorax and thoracoplasty, to "rest" the diseased area or to reduce the size of tuberculous cavities, were common. Typically, a tubercular patient would be hospitalized for a year or more. Given the danger of infection, sufferers were isolated from their normal worlds. Even if their disease was eventually arrested, the personal and social impact of the disease was significant. The possibility of death was very real; sometimes entire families were wiped out by tuberculosis.

Streptomycin comes on the scene

For half a century after Robert Koch's discovery of the tubercle bacillus in 1882 as the cause of tuberculosis, attempts at systemic treatment were made. These treatment approaches began with

Koch's own enthusiastic, but eventually disappointing, use of tuberculin, an inactivated product of the tubercle bacillus, and ranged through the use of sanocrysin, a gold compound, in the 1920s and 1930s. A study that may have been the first placebo-controlled clinical trial in the world proved sanocrysin to be disappointingly ineffective in curing tuberculosis.[29] Transient enthusiasm occurred for proposed cures, which ultimately proved ineffective. An example is the use of turtle serum, thought to be effective because the turtle has antibodies to a type of mycobacterial disease.[30] One disappointment after another led to a pervading skepticism about any proposed new treatment for this persistent and resistant disease. When streptomycin appeared in the wake of penicillin's spectacular wartime success and showed promise in treatment of tuberculosis, it was greeted with suspicion by the older, more experienced phthisiologists.[30]

Very little streptomycin was available at the beginning of 1946. Its distribution to civilians in the United States and England was controlled by central governmental agencies. In early 1946, the entire VA hospital system received only 2 kg per month. General Hawley appointed a "Streptomycin Committee," chaired by Dr. Barnwell, to distribute this scant supply to VA hospitals. Barnwell recruited Dr. Arthur Walker, who had worked on the clinical development of penicillin during the war, to serve as Secretary to the committee and coordinate the streptomycin treatment program. At first, all of the streptomycin was used for nontuberculous conditions such as tularemia. Gradually, the manufacturers succeeded in increasing production. By April 1946, some streptomycin was available to explore treating selected tuberculosis patients.

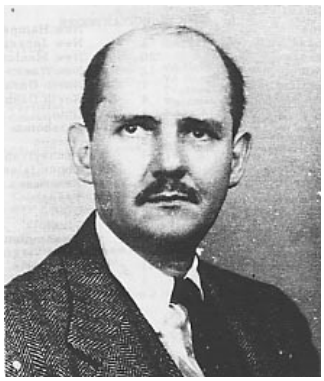


Figure 5.3 Arthur Walker, M.D.

In preliminary clinical trials,[31] streptomycin, which had been discovered in 1944,[32] showed promise against tuberculosis. It was known to inhibit the tubercle bacillus in culture. But despite a few isolated cases successfully treated with streptomycin, no one really knew if clinical tuberculosis would be helped by the drug.

Tuberculosis is a very complex disease. The tubercle bacillus grows slowly and often attacks sites that are not very vascular, so the antibiotic might not reach the bacillus through the blood stream. It walls itself off in "tubercles," surrounded by fibrous tissue with little blood supply. It invades many parts of the body and shows itself in various ways.

The body fights tuberculosis through its immune system. The treatments that had been successful up to that time, such as bed rest, depended on the immune defensive resources of the patient's body.

Patients frequently would improve without specific treatment. Permanent arrests of the disease often occurred, though it was generally felt that people were never completely "cured." Whether streptomycin would alter the course of this complex clinical picture and bring about true cures was doubtful. Barnwell and Walker set out to try to answer that question.[33]

Design of the VA-Armed Forces streptomycin trial

Walker had been part of the central group coordinating wartime studies of penicillin treatment of syphilis. Those studies depended on systematic study of the patient before and during treatment, standardization of a prescribed regimen of treatment and adequate follow-up. Comparison with an untreated control series of patients, or with patients treated with the then-standard arsenical and bismuth regimens, was not a part of these studies. Instead, the investigators drew on their significant personal clinical knowledge about the natural history of syphilis, knowledge believed sufficient to predict the course of the disease without penicillin.[34]

The design for the first VA-Armed Forces study of streptomycin in tuberculosis, begun in 1946, followed the same pattern as that used for the study of penicillin in syphilis: carefully defined study of the patient before treatment, prediction of what the patient's clinical course would be without treatment, standardization of treatment to a single dosage schedule, observation for the effect of treatment on signs and symptoms of tuberculosis, repeated cultures to isolate the tubercle bacillus, observation for treatment complications, and post-treatment follow-up.

In their first report to the American Medical Association Council on Pharmacy and Therapeutics, Barnwell and Walker cited the preliminary reports about streptomycin, especially those already published from the Mayo Clinic. The reports made clear that the widespread VA-Armed Forces clinical study was founded on good evidence that streptomycin was effective in at least some instances:

> "There was thus available to the federal agencies, at the time their investigation was designed, considerable information as to the effectiveness and dangers of streptomycin in the treatment of human tuberculosis. Without this information the investigation would not have been undertaken."[35]

This statement describes the prevailing attitude at the time in the United States. It was the physician's responsibility to do the best thing for the patient. The patient's responsibility was to adhere to the prescribed treatment, generally without participating actively in the therapeutic decision. "Informed consent" for an unestablished treatment was not the norm.

Barnwell and Walker chose seven VA and two military hospitals for their study of streptomycin in tuberculosis. These included VA hospitals at Bronx (N.Y.), Hines (Ill.), Livermore (Calif.), Oteen (Asheville) (N.C.), and three hospitals that have since been closed: Rutland Heights (N.J.), San Fernando (Calif.), and Sunmount (N.Y.). Also included were Fitzsimons General Army Hospital in Denver and the Sampson, N.Y,, Navy Hospital. Only patients selected for the study in these hospitals received the drug. Hospital selection for the first study was based on having doctors knowledgeable about tuberculosis who were eager to cooperate in a study to see what effect streptomycin had on moderately advanced tuberculous disease.

These hospitals were given an allotment of the precious streptomycin that was adequate to treat those patients who qualified for the protocol. Barnwell and Walker worked with representatives of the Army and Navy to establish and follow a common protocol. Requirements of the protocol were:

> "a. That all cases would have been observed for a period of at least sixty days prior to initiation of treatment and that during this period the pulmonary lesion would have become more extensive or, at best, remained stationary;
> b. That tubercle bacilli would have been recently recovered from the sputum or gastric contents and that confirmation of their identity by inoculation into guinea pigs, or by culture, would have been started;
> c. That moderately advanced disease would be preferred but that far advanced disease would be acceptable, provided the patient had an estimated life expectancy of at least twelve months without streptomycin therapy;
> d. That the X-rays would disclose some exudative component, the more the better, in the pulmonary lesion;
> e. That all patients would preferably have been on complete bed rest prior to therapy but, if this was not the case, that they would observe the same degree of physical activity during therapy as was in effect before treatment was started;
> f. That pneumothorax would not be present on the side toward which the treatment was primarily directed;
> g. That no collapse procedures would be initiated during treatment but, if pneumoperitoneum, phrenic paralysis, or contralateral pneumothorax was present prior to treatment, they would be maintained at the preexisting level."[35]

Since the first question to be answered was whether streptomycin really had any effect on the course of tuberculosis, Barnwell and Walker and their colleagues first decided to use a dosage schedule that could be expected to maintain blood streptomycin levels over the course of 24 hours. Based on previous experience with penicillin, patients in the first study received a daily dose of 1.8 grams of streptomycin, 0.3 grams intramuscularly every four hours. As they state in their early paper describing the study:

> "These decisions concerning dosage and duration of treatment were admittedly arbitrary for there were no data on which to base an informed judgment but, in order that the study have any statistical significance, it was considered essential that this first group of patients be treated in accordance with a single regimen."[33]

Barnwell and Walker visited the study hospitals to review the patients chosen for the study and to assist in meeting the criteria. They soon found that the majority of patients in VA tuberculosis wards had far-advanced disease, so a larger fraction than planned of these patients were included in the study.

The question of controls

From the beginning of this study, discussion and worry centered around the use of controls. Some felt that concurrent untreated controls were essential. However, withholding the drug raised ethical

concerns, once clinicians became convinced that it worked, even though that hadn't been proven. Finding it impractical to include prospectively randomized controls in their study, Barnwell and Walker and their advisors then substituted two other types of controls:

a. Use of the patient as his own control, and
b. Use of untreated patients, similar clinically, from a time before streptomycin was available.

Not everyone was satisfied, however, with the decision to omit the use of concurrent randomized controls. Gilbert Beebe, Ph.D., a statistician who headed the National Research Council's Follow-up Agency (Chapter 4), met with Barnwell and urged the use of untreated controls.[36] Heated discussion of the issue of controls occurred at the third Streptomycin Conference in 1947, but the issue was not resolved. The following exchange between Dr. Walker and Paul Densen, D.Sc., a distinguished statistician who had joined VA Central Office, is recorded in the minutes:

> "Dr. Densen: From the statistical research end, it would be better to work only five cases in many different ways rather than to enlarge such a study to 50 cases. If you do five cases intensively, and do five cases without streptomycin, on which you get the same kind of laboratory observations, you will have a better series statistically than if you do all 10 cases on streptomycin."
>
> "Dr. Walker: You and I have been arguing on opposite sides of the control question for the last few days."[37]

After this discussion with the statisticians, the clinicians met in executive session, without the statisticians, and decided not to include untreated controls.

The streptomycin conferences begin

In December 1946, those involved in conducting the streptomycin trial met in Chicago for the first of what proved to be a 25-year series of conferences. In addition to the VA, Army and Navy participants and Corwin Hinshaw, M.D., of the Mayo Clinic, the first physician to use streptomycin in patients, attended. Other participants included Esmond Long, M.D., of the Phipps Institute in Philadelphia, who later led an important U.S. Public Health Service study (discussed below), and C.J. Van Slyke, M.D., Medical Director of the National Institute of Health.

At this first meeting, participants brought the records and biweekly chest x-ray films of the patients they had treated. As Dr. Walker described it, "34 individuals sat in a tight semicircle for three days gazing devotedly at x-ray view-boxes." The assembled group read the series of x-rays from each of 135 patients, and wrote down their opinions about changes in the tuberculous lesions. A statistician from VA Central Office statistics group then tabulated the opinions.

The proceedings of this conference and of all of the later conferences were published by VA and distributed widely.[38]

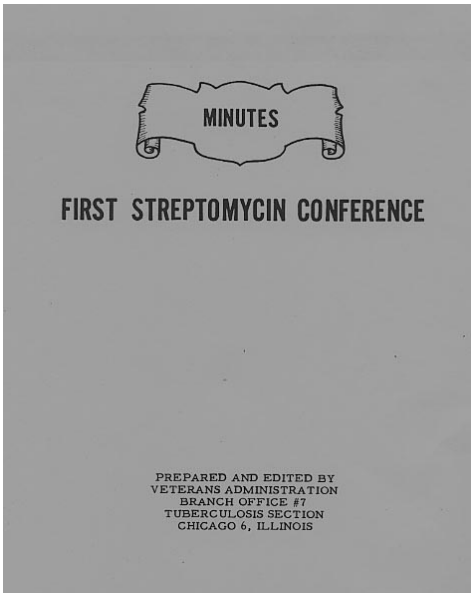


Figure 5.4. Cover of the published minutes of the First Streptomycin Conference

Results of the first VA-Armed Forces streptomycin study

Since the organizers of the study had little idea about the expected outcome, the first patients were studied very thoroughly. They received chest x-rays, many of them stereoscopic, every two weeks during treatment. Auditory and vestibular function and screens for renal or hepatic toxicity were frequently assessed. Bacteriologic response was monitored, and blood streptomycin measured. Careful clinical records were kept.[33]

Clinically, the initial improvement in the first group of 223 patients was impressive. The investigators were enthusiastic about their patients' increased sense of well-being. Most patients (85 percent) had improved appetites and gained weight. Most (73 percent) who had fever became afebrile. Sputum production, cough and the number of tubercle bacilli in the sputum decreased. Of this first group of patients, 43 percent became bacteriologically negative during the 120 days of streptomycin treatment.

But there were also adverse effects. Most frequent and disturbing (92 percent) was vestibular (inner ear) damage, which disturbed the patient's balance, and this persisted after treatment, though many patients adapted to it. The caloric test for vestibular function was affected in 77 percent, but only 0.5 percent had objective hearing loss; 67 percent developed casts in their urine and 70 percent developed eosinophilia.

Encouraged by the results but suspicious of chest-film readings by those clinicians participating in the study, Barnwell and Walker sought a more objective assessment. For this, they recruited a jury of seven tuberculosis experts chosen by the President of the American Trudeau Society, the premier society for the study of tuberculosis. These seven men met for six days in May 1947 to read and compare films. They were presented with blinded film sets from patients with and without

streptomycin treatment, each set containing three films. The first two films in each set were taken at a two-month interval, the third after a four-month interval. In the case of treated patients, the first two-month interval was the pretreatment observation period. The first x-ray reviewed was taken two months before treatment began and the second immediately before treatment. The second, four-month interval was the period of streptomycin treatment in the treated group. The jury of experts evaluated interval changes in 222 lesions in 131 patients during the two months just prior to streptomycin treatment and during the four months of streptomycin administration.

The corresponding interval changes were also judged in 142 lesions in 88 "historical control" patients, patients at the same hospitals who met the criteria of the study but who had been treated before streptomycin became available.

Table 5.1. Chest film review by panel of experts. Review of 222 lesions in 131 patients treated with streptomycin and of 142 lesions in 88 historical control patients.

	Percent of exudative lesions	
Interval	Treated (n=222)	Untreated (n=142)
2 mo. before "treatment"		
Worse	36.9	7.0
No Change	34.2	57.1
Better	28.9	35.9
4 mo. during "treatment"		
Worse	0.5	4.2
No Change	14.5	65.6
Better	85.0	30.2

The results of their review were dramatic (Table 5.1). Firstly, it looked as if the historical controls chosen from the participating hospitals were, on average, less ill than the treated patients. Fewer of their exudative lesions worsened over a two-month period than did those in the study patients during the two-month pretreatment observation period. Among the untreated patients, the natural history of the illness was predictably stable, with about as many lesions worsening or improving over the next four months as during the first two months. On the other hand, in the treated patients, exudative lesions were much more likely to improve during the four months of streptomycin than during the pretreatment period. Only one of the 222 lesions evaluated in the treated patients worsened during treatment.

A more extensive, but less objective, analysis included all of the biweekly films of all 223 patients (Table 5.2). In this study, physicians at the various participating hospitals read the films. Again, a dramatic improvement occurred during the period of streptomycin treatment.

Resistance to streptomycin

Eight percent of the patients in Table 5.2, after an initial improvement, began to do worse while still receiving streptomycin. This pattern would not have shown up on the "expert panel" readings, as that panel didn't review films taken during the treatment course. The pattern of improvement followed by worsening suggested that resistance of the organisms to streptomycin was developing. Bacteriological analysis confirmed that 44 percent of the patients' organisms had become

Table 5.2. Chest x-ray readings by physicians at the patients' hospitals (223 Patients)

	Percent of Patients		
	Before Rx	During Rx	After Rx
Progression	75.3	0.5	16.4
Stationary	17.1	6.5	44.1
Regression	7.6	84.7	39.5
Regression, then progression	NA	8.3	NA

moderately or markedly resistant to streptomycin by the end of two to three months' treatment at 1.8 grams/day and 65 percent were resistant at four months.[33] This finding, that the tubercle bacillus became resistant to streptomycin as treatment progressed, and that resistance was associated with a reduced clinical response to the drug, was a uniform finding in all three streptomycin studies described in this chapter.

Conclusion: Streptomycin is effective in treating pulmonary tuberculosis

In May 1947, the VA-Armed Forces group had completed treatment of 543 cases, all having received 1.8 or 2 grams of streptomycin per day, and were convinced that streptomycin does, in fact, have a beneficial effect in treatment of tuberculosis. Expert panels confirmed this conclusion in 1947.

Results in other types of tuberculosis

In addition to the study of pulmonary tuberculosis, by far the most prevalent type of the disease, the group studied other forms, following a variety of protocols tailored to each condition. By the time of their first publication in November 1947, the group could clearly recommend streptomycin in tuberculous cutaneous sinuses, tuberculous lymphadenitis, tracheobroncial and laryngeal tuberculosis, and tuberculosis of the tongue, tonsils, intestine and peritoneum. In fact, the results were so favorable that they never were able to complete the protocols planned for those conditions—there were no longer enough patients. Other extrapulmonary tuberculosis, of the urinary system, bone, joints and pericardium, showed less clear-cut benefit. Even miliary or meningeal tuberculosis, previously a death sentence, sometimes yielded to streptomycin.

Informing practitioners of study's results

At the third VA-Armed Forces Streptomycin Conference, held in May 1947, participants discussed the best way to let others know about their early results. Dr. Walker felt strongly that participants from each hospital should publish their own results. Barnwell suggested a summary article, followed by articles from individual hospitals. This was the plan eventually followed. There was concern, however, that information dissemination shouldn't wait for the formal publication process. As Barnwell said:

> "There is one thing that we have been warned about repeatedly in all matters of this sort, and that is that we should get this thing to the profession before it gets to the layman. We have already put the profession in a position of having to keep strict silence on this program. Items have been appearing in lay magazines and the daily press. It is high time we got it to the profession through their own journals, instead of putting the profession in the position of having patients read about streptomycin in the

newspapers."[39]

W. Van Winkle, M.D., who represented the American Medical Association, suggested that there be a brief statement in *JAMA*:

> "It seems to me that we have a twofold problem, one of acquainting the general profession, and the second of acquainting those who are treating tuberculosis patients, with the details of the results. The first thing is most important at the present time; that is, to acquaint the general profession with streptomycin. I would urge that some sort of statement be published .... The A.M.A. is receiving from 10 to 12 letters a week asking about streptomycin in tuberculosis, and we have no good reference to give them."[40]

The first of a series of such statements to the profession, officially authored by the Chief Medical Officers of the VA, Army and Navy but presumably written by Walker and Barnwell, was published as a report to the AMA Council on Pharmacy and Chemistry in the November 8, 1947, issue of *JAMA*. It concluded that:

> "The findings of Hinshaw and his several collaborators have been confirmed. Streptomycin is a useful adjunct in the treatment of tuberculosis."[35]

The primary publication of this first VA-Armed Forces study of streptomycin in tuberculosis presenting results in the first 223 patients was published that same month in the *American Review of Tuberculosis*.[33]

Later studies by the VA-Armed Forces group

By the May 1947 meeting, it was clear that the side effects of streptomycin, especially the damage it caused to the vestibular system, were troubling. Also, a large fraction of the treated patients now harbored tubercle bacilli that were resistant to streptomycin. These patients and those who caught the disease from them could no longer benefit from streptomycin. The VA-Armed Forces collaborative group decided to branch out, to try different treatment schedules in a search for one that would have a therapeutic effect, but with less toxicity and drug resistance.

They compared the 2-gram-per-day dose they had been using with 1 gram per day. Again, they did not use true randomization. Instead, the group divided itself for comparison, with some hospitals continuing the 2 gram/day regimen, others changing to 1 gram/day. They found the results comparable, but with less toxicity when 1 gram/day was administered. They provided this information in an addendum to their primary November 1947 publication.[33]

Figure 5.5. Executive Committee Meeting, VA-Armed Forces Cooperative Study on the Chemotherapy of Tuberculosis, VA Hospital, Sunmount, N.Y., September 10, 1959. Clockwise: Dr. William Harris, VA Hospital, Salt Lake City; Dr. William Hentel, VA Hospital, Albuquerque, N.M.; Dr. H.E. Walkup, VA Hospital, Oteen, N.C.; Dr. Patrick Storey, VA Hospital, Baltimore; Dr. B. Ramin, Regional Office, Boston; Dr. W. Spencer Schwartz, VA Hospital, Oteen, N.C.; Dr. R.H. Schmidt Jr., VACO; Dr. Edward Dunner, VACO; Mrs. Dorothy Livings, VACO; Dr. N. D'Esopo, VA Hospital, West Haven, Conn.; Dr. A. Falk, Consultant, St. Paul, Minn.; Capt R.G. Streeter (MC) U.S. Navy; Dr. Maurice Small, VA Hospital, East Orange, N.J.; Dr. Williamm. Feldman, VACO.

The many subsequent VA-Armed Forces trials of treatment regimens for tuberculosis used comparison groups but always compared the current "best" treatment with the proposed new treatment. At first, the comparison was among hospitals that adopted different "arms" of the study. But in 1948, they introduced comparison groups within the hospitals, randomizing by the patient's hospital number. Later, they adopted true randomization. The consortium of investigators continued to work together, examining new opportunities for the treatment of tuberculosis and meeting annually until 1972. The group of investigators and their particular interests and areas of expertise expanded. Specialty committees met, and an Executive Committee determined the overall course of the studies.

The MRC streptomycin study

In 1946, the British National Health Service met an even more difficult challenge than did VA. Streptomycin was in such short supply that in all of Great Britain there was only enough to treat 50 patients with pulmonary tuberculosis.[41] Taking this problem as an opportunity, A. Bradford Hill, an eminent statistician, and Phillip D'Arcy Hart, the Director of the Tuberculosis Research Unit of the Medical Research Council (MRC), persuaded the MRC to sponsor a truly randomized clinical trial of tuberculosis.

Study design

In the MRC study, patients who met very narrow criteria, as judged by a central committee, were referred to cooperating hospitals. They were randomized either to a ward where they would receive

streptomycin or to one where they would not. As is commonly done today in cooperative clinical trials, randomization was by a "statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill."[42] Unlike present-day practice, however, none of the patients were told they were participating in a research protocol.

Patients in the streptomycin group received 2 grams/day, 0.5 gram intramuscularly every six hours, for four months—essentially the same dosage schedule used in the first VA-Armed Forces study. In all respects except administration of streptomycin, the care of the streptomycin group and the control group was the same. All patients in both groups were kept on bed rest for the six-month study period.

As in the VA-Armed Forces study, a panel of experts read the sequential x-ray films of the patients, blinded to their treatment group. The design of this review was somewhat simpler than in the VA-Armed Forces study, but the outcome was very similar.

Results

Just as in the larger and "looser" VA study, the MRC group found that the early response to streptomycin was dramatic: at six months, only 7 percent of the streptomycin-treated patients had died, compared with 27 percent of the controls. Of those still living, only 18 percent of the streptomycin-treated patients had deteriorated clinically, compared with 46 percent of the controls. Radiological improvement had occurred in 69 percent of the streptomycin patients, but in only 33 percent of the controls. Of the streptomycin patients, 15 percent had no tubercle bacilli in their sputum or gastric washings; in only 4 percent of the control series was that the case. Notably, however, of those in the streptomycin-treated group who still harbored tubercle bacilli, 85 percent of those bacilli were resistant to streptomycin.[42]

The USPHS streptomycin study

In 1947, the U.S. Public Health Service (USPHS) began planning its own study of streptomycin in pulmonary tuberculosis. Heading this study was Carroll Palmer, M.D., a statistician who had argued unsuccessfully for the use of untreated controls in the original VA study.[43] Its senior physician was Esmond R. Long, M.D., who was also involved in the VA studies. Participants included Dr. Emil Bogen of Olive View Sanatorium in Southern California, who, as a consultant at the San Fernando VA Hospital, was also an active participant in the VA study. Other "crossover" participants included John Barnwell, M.D., Corwin Hinshaw, M.D., Ph.D., Walsh McDermott, M.D., Paul Bunn, M.D., Nicholas D'Esopo, M.D., and William Tucker, M.D..[44]

Study design

At the fifth VA-Armed Forces Streptomycin Conference, held in April 1948, Shirley H. Ferebee, the USPHS statistician who coordinated the study, presented the protocol to the VA group.
The USPHS group planned five studies, the first of which asked: "How useful is streptomycin in the treatment of tuberculosis?" The plan for that study was to enroll 1,000 patients with pulmonary

tuberculosis, half of whom would receive streptomycin in addition to other indicated treatment. The controls would "receive any therapy indicated other than streptomycin." In her presentation, Ferebee emphasized the following conditions: All cooperating investigators must agree to adhere to the protocol and make and record observations in the prescribed manner; a panel of experts would judge the suitability of patients for the study; the central study office would make assignment to treatment group by chance and would evaluate the results using "quantitative" observations.[45]

Patients with all types of tuberculosis and treatments were included. Even prior treatment with streptomycin was permitted, but accounted for only a small number of patients. Streptomycin dosage (about 1.4 grams/day) was somewhat smaller than used in the original VA-Armed Forces and MRC studies but more than the 1 gram/day dose reported by the VA-Armed Forces group to reduce complications, compared with 2 grams/day, without affecting outcome. Unlike the original VA-Armed Forces and MRC studies, in which streptomycin was given for four months, it was given for three months in the USPHS study.

The idea behind this trial design was to conduct a field study, assessing streptomycin effects under all sorts of tuberculous conditions, in contrast to the VA-Armed Forces and MRC studies, in which patients had been selected for suitability. The inclusion of randomly selected control patients who did not receive streptomycin was key to this study. This was by no means uncontroversial. Even the establishment of a central "Appeals Board" to approve deviations from the protocol didn't reassure those who questioned the use of untreated controls. J. Burns Amberson, M.D., who, ironically, had been leader of a placebo-controlled study of tuberculosis treatment in the 1920s (which proved sanocrystin to be useless in treatment of tuberculosis) opposed the use of a central group to supplant the physician's clinical judgment:

> "As a matter of fact I do not believe it is possible to give a definition (of life threatening disease) which would cover all the possibilities. Fundamentally, it rests on the judgment of the physician who is treating the case and who knows the patient best. He is in a far better position than anyone else to make the decision. If he is capable of undertaking a clinical investigation of therapy, he is certainly capable of assuming the responsibility for such judgment."[46]

In the end, a total of 23 of the 271 control patients received streptomycin, 12 of them with approval of the Appeals Board and 11 of them without such clearance. These were partly balanced by seven of the 270 patients who were randomized to streptomycin but who refused the drug. The statisticians were able to deal with these small numbers of deviations from the protocol and to present a definitive result, assessing each patient at the end of a one-year observation period.

Results

Like the VA-Armed Forces and MRC study investigators, the USPHS investigators found that improvement occurred more frequently in the streptomycin group than in the control group by all of the criteria they examined: mortality, temperature, body weight, conversion of sputum culture and x-ray appearance of the thorax. These results were statistically significant, and, it was believed, would convince the doubters about streptomycin's efficacy when they were published in 1950.[44]

Table 5.3. Characteristics of the three major trials of streptomycin efficacy in pulmonary tuberculosis

	VA-DOD	MRC	USPHS
Date planning begun	May 1946	Sept. 1946	July 1947
Date first patients entered	July 1946	Jan. 1947	Nov 1947
Date series completed	May 1947	April 1948	May 1950
Date of primary publication	Nov. 1947	Oct. 1948	Nov. 1950
Study design:			
Number of study sites	7	6	14
Type of institutions	VA&military	public	variable
Controls	Pre-rx obs of pt, historical conts	Prospective, randomized	Prospective, randomized
Screening of patients	Local	Central	Central
Chest x-ray evaluation	Impartial jury	Impartial jury	Impartial jury
Data analysis	Central	Central	Central
Patient characteristics:			
Number given streptomycin	223	55	270
Number of concurrent controls	None	52	271
Ages	97.3% < 46y	Under 30	81% <45y
Gender	98.2% male	40% male	53% male
Race	74.8% white	not stated	61% white
Restrictions on clinical type	Exudative lesions	New disease	Not minimal
	No collapse Rx	No collapse	Any assoc Rx
	Life expect.>1yr	Progressive	Not terminal
% with positive cultures on entry	100	100	100
% with fever on entry	72	70	66
% with elevated ESR on entry	83	95	not stated
Treatment protocol:			
Pre SM observation	60 days	1 week	Variable
Days on streptomycin	120 days	4 months	91 days
Minimum post-Rx observ.	120 days	2 months	9 months
Daily streptomycin dose	1.8 grams	2 grams	20mg/kg
Dosage schedule	0.3gq4h	0.5gq6h	3 daily doses
Surveillance:			
For complications			
Auditory	Yes	Not stated	Not stated
Vestibular	Yes	Variable	Not stated
Renal	Yes	No	Yes
Hepatic	Yes	No	No
Hematologic	Yes	No	Yes
For clinical response			
Chest xray	q2wk	Monthly (?)	q3mo(?)
TPR	q4h	yes	qd
ESR, wt	q2wk	Yes	Yes
Physical exam	q2wk	Yes	q3mo
Nude photos	Rx beg and end	No	No
For bacteriological response			
Culture	q2wk	variable	7 in 1 year
Sensitivity to SM	variable	variable	all positives
Blood SM concentration	variable	not done	not done

The use of untreated control patients in these studies

The original VA-Armed Forces streptomycin study has been criticized for its lack of suitable controls. The planners of the study were aware that simultaneous, untreated controls were desirable, but they decided against using them. In their primary report of their study, the VA-Armed Forces investigators explained:

"It was the original decision of the Committee to have the Units select suitable cases

> and then divide them at random into two groups, the one to be treated with streptomycin, the other to provide controls. It seemed a feasible procedure at the time. The very scanty supplies of streptomycin, and the real ignorance of its effectiveness, made it reasonable to leave half the patients without treatment or, rather, to treat them by other methods than streptomycin. In retrospect, it would have been highly desirable to do this ...."[33]

But by the time the study had been launched, there was enough streptomycin to treat all eligible patients. The authors then went on to rationalize the approach they had taken:

> "The purpose of controls, in such a situation as this, is to compare the results of one form of therapy with another. In so far as a comparison of the effects of bed-rest upon pulmonary tuberculosis is concerned, these cases may reasonably be said to serve as their own controls."[33]

When the MRC group decided to include untreated control patients, they faced a simpler ethical situation: At that time, there really was a shortage of streptomycin, and only a few patients could be treated, whatever study design was adopted:

> "The selection of this type of disease constituted full justification for having a parallel series of patients treated only by bed-rest, since up to the present this would be considered the only form of suitable treatment in such cases. Additional justification lay in the fact that all the streptomycin available in the country was in any case being used, the rest of the supply being taken up for two rapidly fatal forms of the disease, miliary and meningeal tuberculosis."[42]

In addition, in the austere medical climate of post-war Britain, even the patient selected for the study and randomized to the control group benefited:

> "When a patient had been accepted as suitable, request was made through the local authority for admission to one of the streptomycin centers; in spite of long waiting-lists these patients were given complete priority, and the majority were admitted within a week of approval."[42]

The rationale was different for using untreated controls in the USPHS study. Its planners and the Study Section that reviewed this very expensive project felt that a large, controlled study was necessary to establish once and for all whether streptomycin had a real effect:

> "Previous investigations had indicated a distinct and often dramatic improvement in many cases treated with streptomycin. However, further evidence was essential to distinguish the effect of the drug from the vagaries of the disease and the effect of other treatment. The Study Section agreed that the major portion of the funds specifically appropriated by the Congress for streptomycin research could best be employed in a rigorously planned investigation designed to determine, through the use of concurrent controls, the effect of adding streptomycin to other therapeutic measures."[44]

A central question about the USPHS study was the ethical justification for leaving a group of patients untreated with an antibiotic that was readily available and that might have helped them. The VA and MRC studies, each in its own way, had already shown that addition of streptomycin to standard treatment in pulmonary tuberculosis was superior to standard treatment alone. But the VA-Armed Forces study was statistically "loose," and the MRC study had a relatively small number of patients. Both of the earlier studies had been limited to patients with particular forms of a most variable disease. Perhaps the results of the VA-Armed Forces and MRC studies had not been widely accepted at the time the USPHS study began. In the past, there had been so many disappointments, so many "turtle serum"-type enthusiasms, that academic leaders and responsible public officials may have felt the need to be sure of their ground before advocating the use of a treatment that was also toxic to many patients.

On the other hand, streptomycin was becoming widely used before the results of the USPHS study were published in 1950 and investigators were moving on to other treatments (Table 5.4). By the time the USPHS study had completed patient intake, combined therapy with streptomycin and paraaminosalycilate (PAS) was already under study by the VA-Armed Forces and MRC groups and was proving to be superior to streptomycin alone. Both groups published those results before publication of the USPHS study (which did not use the combined therapy). The USPHS study may have suffered the fate of other studies for which planning, funding and preparation take a long time: it may have become obsolete by the time its results were published.

Table 5.4. Reports involving antituberculosis chemotherapeutic agents cited under "Tuberculosis - therapy" in *Index Medicus*. Entries are the number of citations mentioning the agent in their titles.

	1947	1948	1949	1950
Streptomycin	44	120	102	86
PAS	4	10	32	45
Combined agents	3	3	8	12
Thiosemicarbazones	0	2	8	42
Other antibiotics	2	13	12	10

One must assume that the investigators in the USPHS study, some of the leaders of academic phthisiology, still had sufficient doubt about the question of streptomycin's efficacy to justify staying with the study to its completion.

The use of untreated, or placebo-treated, controls continues to be controversial in some situations; debate continues on this issue.[47]

"Informed consent" by patients in these studies

Even though the concept of informed consent by experimental subjects has its roots in the reaction to Nazi atrocities that claimed to be carried out in the name of science, it was not a widespread concept in the late 1940s. The organizers of the USPHS study faced the dilemma of withholding streptomycin from randomly assigned patients by making access to the study, and its funding, available only to investigators who were willing to study untreated control patients. They also provided an appeals mechanism for desperate cases. They dealt with the problem of pressure for treatment from patients in the control group by simply not informing the patients that they might benefit from streptomycin treatment.

The untreated patients in the MRC randomized controlled study also didn't know that they were a part of a randomized study: "Patients were not told before admission that they were to get special treatment."[42] They were placed on different wards from treated patients and were probably unaware of the possibility of streptomycin treatment. In the MRC study, it was easier to justify randomization of patients to the arms of the study, because the shortage of streptomycin in Britain at that time was so severe that patients who were not in the study did not have access to streptomycin treatment. Nevertheless, the planners of the study apparently did not feel obligated to inform patients about the goals and procedures of the study or to obtain their permission. As stated in the study report:

> "It was important for the success of the trial that the details of the control scheme should remain confidential. It is a matter of great credit to the many doctors concerned that this information was not made public throughout the 15 months of the trial, and the Committee is much indebted to them for their cooperation."[42]

The VA group was dealing with a patient population that was more aware of their options. Patients needed to be told about the drug and its risks as well as its benefits, though no formal consent process was required. At the January 1947 meeting of participants in the VA-Armed Forces study, Dr. Walker told the group:

> " It has seemed wise to have each patient who has received streptomycin, sign some general statement. A copy of something you might use for that purpose is enclosed in your folder."[48]

S.T. Allison, M.D., Chief of the Medical Service at the Rutland Heights (N.J.) VA Tuberculosis Hospital, commented at the VA-Armed Forces study participants' meeting in May 1947: "This primarily is a research problem, but we in the field have to more or less sell this experiment to the patient." Allison went on to comment, in response to the suggestion that very small doses of streptomycin be tried:

> "If we are going to get patients to subject themselves to streptomycin treatment, we have to show some results or we won't get the patients. I know that in my hospital, where we have 500 patients under treatment for tuberculosis, it is one big family, and they are interested in results. If they see a group of patients putting on weight and getting better, they will be for streptomycin. On the other hand, if it is purely experimental, if we don't get results, one patient will say, 'So-and-so didn't get any benefit, so I won't take it. I won't subject myself to this treatment.' We have got to think not only of the research problem but of the clinical problem as well."[39]

Nevertheless, the use of a formal consent form appears to have been optional, and it is uncertain whether VA patients realized that they were part of a research protocol.

This issue of patient autonomy and its associated transfer of responsibility from the physician to the patient is one that still confronts clinical researchers and those who oversee their work.

Later studies of tuberculosis treatment

A major difference between the original VA-Armed Forces study and those of the MRC and USPHS was that the original VA-Armed Forces investigation was planned by the investigators themselves, with little input from statisticians. As time went on and they gained more experience, the VA-Armed Forces group gradually came to accept statistical guidance, although they never carried out a placebo-controlled study.

Gradually, VA studies and those of the MRC and USPHS grew more alike. In April 1948, VA investigators began testing paraaminosalicylic acid (PAS) in combination with streptomycin, using the streptomycin-alone regimen for the control series. As soon as the streptomycin-PAS regimen was shown to be superior, it was taken as the control against which new treatments were tested. The MRC and USPHS groups used similar strategies, once the original question of efficacy of streptomycin was established. They no longer studied untreated control patients, but instead compared patients receiving the new treatment with those receiving an established one.

After feeling their way along in the early days, learning as they gained experience with their studies, negotiating with the statisticians, and coping with the realities of human behavior, in 1960 VA investigators established their concept of the essential principles of a clinical trial:

1. The design of the trial is of critical importance.
2. Ethical considerations are essential, particularly in the selection of regimens to be investigated.
3. The "experimental" regimen to be studied should be compared with a "control" series, usually the best known available form of therapy.
4. Such comparisons preferably should be concurrent, not retrospective.
5. Assignment to treatment should be by a method of random selection, as free from possible bias as the circumstances permit.
6. The number of patients studied should be sufficiently large to permit valid deductions to be drawn.
7. Every effort should be made to ensure that observations of results are as objective and uniform as possible.
8. Statistical guidance should be provided at all stages of the study, from design to rigid statistical evaluation of results.[49]

These principles form the basis for today's extensive and productive VA Cooperative Studies Program.

References

1. Daniel, T.M., "An immunochemist's view of the epidemiology of tuberculosis." in *Prehistoric Tuberculosis in the Americas*, Buikstra, J.E., Editor. 1976, Department of Anthropology, Northwestern University: Evanston, IL 40-41.

2. Jones, R.S., *The History of the American Legion*. Indianapolis and New York: The Bobbs-Merrill Company, 1946, 125-126.

3. Hawley, P.R., "The tuberculosis problem of the Veterans' Administration." *Am Rev Tuberc*, 1947. **55**: 1-7.

4. *Tuberculosis Service*. Washington, D.C.: Veterans Administration, 1945

5. Edwards, H.R., "The National Tuberculosis Association and its interest in the tuberculous veteran." *Am Rev Tuberculosis*, 1947. **55**: 8-16.

6. Matz, P.B., "The effect of climate upon the treatment of pulmonary tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 1150-1159.

7. Matz, P.B., "The surgical treatment of pulmonary tuberculosis in the United States Veterans' Bureau." *Am Rev Tuberculosis*, 1929. **20**: 809-832.

8. Matz, P.B., "The end-results of The surgical treatment of pulmonary tuberculosis." *Am Rev Tubercul*, 1936. **33**: 533-548.

9. Veterans' Bureau Medical Council, "Report of Group of Tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 840-841.

10. Matz, P.B., "Statistical studies on tuberculosis in the United States Veterans' Bureau." *Medical Bulletin of the Veterans' Bureau*, 1926. **2**: 793-794.

11. Forbes, C.F., *Annual Report of the Director, United States Veterans' Bureau*. Washington, DC: Veterans Bureau, 1922, 31.

12. Hines, F.T., *Annual Report of the Administrator of Veterans' Affairs*. Veterans Administration, 1941, 7-8.

13. Carr, B.W., "Bone tuberculosis treated by actinotherapy." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 1003-1004.

14. Fisher, E., "Heliotherapy in the treatment of laryngeal tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 1066-1068.

15. Matz, P.B., "Tuberculosis in mental hospitals." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 490-491.

16. Matz, P.B., "The effect of intercurrent diseases on the clinical course and the hospitalization period of cases of pulmonary tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 998-1002.

17. Marcley, W.J., "End results of pulmonary tuberculosis-A study of 500 cases." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 128-133.

18. Park, W.E., "History of tuberculosis." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 692-699.

19. Carman, W.L., "Use of actiniotherapy with results of treatment in a case of lupus vulgaris." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 815-817.

20. McKnight, J.L., "Generalized tuberculous adenitis, with report of case." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 725-727.

21. Benedict, C.C., "Pericarditis complicating pulmonary tuberculosis with report of case." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 789-797.

22. Buckley, R.C., "Tuberculous ulcer of duodenum-Case report with postmortem findings." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 228-230.

23. Smith, R.W., "Paramount importance of early diagnosis in treatment of tuberculosis of spine." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 1226-1230.

24. Starns, C.E., "The importance of proper history taking in tuberculosis hospital." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 450-452.

25. "The tuberculous patient." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 505-507.

26. Hines, F.T., *Annual Report of VA Administrator*. 1941, 1-3.

27. Maisel, A.Q., "The veteran betrayed: How long will the Veterans' Administration continue to give third-rate medical care to first-rate men?" *The Reader's Digest*, April, 1945, 45-50.

28. Adkins, R.E., *Medical Care of Veterans*. Washington, DC: Government Printing Office, 1967, 174.

29. Amberson, J.B., McMahon, B.T. and Pinner, M., "A clinical trial of sanocrysin in pulmonary tuberculosis." *Am Rev Tuberculosis*, 1931. **24**: 401-435.

30. Interview with Nicholas D'Esopo, M.D., December 6, 1995 at American Lung Association offices in Hamden, CT.

31. Hinshaw, H.C. and Feldman, W.H., "Evaluation of chemotherapeutic agents in clinical tuberculosis." *Am Rev Tuberculosis*, 1944. **50**: 202-213.

32. Schatz, A., Bugie, E. and Waksman, S.A., "Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria." *Proc Soc Exp Biol Med*, 1944. **55**: 66-69.

33. Barnwell, J.B., Bunn, P.A. and Walker, A.M., "The effect of streptomycin upon pulmonary tuberculosis." *Am Rev Tuberc*, 1947. **56**: 485-507.

34. Hobby, G.L., *Penicillin: Meeting the Challenge*. New Haven and London: Yale University Press, 1985, 156-157.

35. Streptomycin Committee, "The effects of streptomycin on tuberculosis in man, report to the Council on Pharmacy and chemistry." *JAMA*, 1947. **135**: 634-641.

36. Interview with Gilbert Beebe, P.D., June 1, 1994 at a hotel lobby in Washington, DC.

37. "Minutes." *Third Streptomycin Conference*. May 1-3, 1947. St. Louis, Mo.: VA Branch Office, St. Louis. Mo, 1947, 125.

38. "Minutes." *First Streptomycin Conference*. December 12 -14, 1946. Chicago, IL: VA Branch Office #7, Chicago, IL, 1946,

39. "Minutes." *Third Streptomycin Conference*. 5/1-3/47, 1947, 128.

40. "Minutes." *Third Streptomycin Conference*. 5/1-3/47, 1947, 130-131.

41. Hill, A.B., "Suspended Judgement: Memories of the British streptomycin trial in tuberculosis." *Controlled Clinical Trials*, 1990. **11**: 77-79.

42. Marshall, G., Blacklock, J.W.S., Cameron, C., Capon, N.B., Cruickshank, R., Gaddum, J.H., Heaf, F.R.G., Hill, A.B., Houghton, L.E., Hoyle, J.C., Raistrick, H., Scadding, J.G., Tyler, W.H., Wilson, G.S. and D'Arcy, P., "Streptomycin treatment of pulmonary tuberculosis." *Brit Med J*, 1948. **2**: 769-782.

43. Marks, H.M., *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990*. Cambridge: Cambridge University Press, 1997, 122.

44. Long, E.R. and Ferebee, S., "Controlled Investigation of Streptomycin Treatment in Pulmonary Tuberculosis." *Pub Health Reports*, 1950. **65**: 1421-1451.

45. Ferebee, S.H. "Report on the USPHS Streptomycin Study Program." *Fifth Streptomycin Conference*. April 15-18, 1948. Chicago, IL: Veterans Administration Branch Office, Chicago, IL, 1948, 49.

46. Letter from J.B. Amberson to E.R. Long, cited in Reference 43, page 124,

47. Rothman, K.J. and Michels, K.B., "The continuing unethical use of placebo controls." *New Eng J Med*, 1994. **331**: 394-398.

48. "Minutes." *Second Streptomycin Conference*. January 23-24, 1947. Chicago, IL: VA Branch Office #7, Chicago, IL, 1947b, 88.

49. Tucker, W.B., "The evolution of the cooperative studies on the chemotherapy of tuberculosis of the Veterans Administration and Armed Forces of the U.S.A." *Adv Tuberc Res*, 1960. **10**: 1-68.

(Intentionally Blank)

Chapter 6. The Atomic Medicine Program and the Birth of Nuclear Medicine

One VA research area that took off quickly after World War II was research in the use of radioisotopes. During the autumn of 1946, Major General Paul R. Hawley, M.D., the Chief Medical Director, became deeply concerned about the problems that atomic energy might create for VA because of the possibility of nuclear warfare. He held a conference in his office on August 7, 1947, attended by key VA and military health officials, including officers who had worked on the Manhattan Engineering Project.[1] Attendees included Lt. Gen. Leslie R. Groves, Commander, and Col. James Cooney, Chief Medical Officer, of the Manhattan Engineering District, the organization that developed the atomic bomb. Also attending were Maj. Gen. Raymond Bliss, Surgeon General, U.S. Army; Rear Admiral W.L. Wilcutts, Deputy Surgeon General, U.S. Navy; Maj. Gen. Malcolm Grow, Air surgeon, U.S. Air Force; Leonard Scheele, M.D., Surgeon General, U.S. Public Health Service; and George Marshall Lyon, M.D., who was the medical officer for much of the early atomic bomb testing that took place on Bikini Island in the Pacific.

George Lyon and the Atomic Medicine Program

Dr. George Lyon (Figure 3.6), a pediatrician from West Virginia, had been assigned to the Manhattan Project as a naval officer and was the ranking medical officer at the Bikini tests in the Pacific. Soon after Bikini, Lyon became VA's expert on atomic energy. When he left the Navy, he retained the records of the military personnel who had been exposed in the various atomic tests. These were stored in a locked file in his office; when he left Central Office in 1956, they went with him.[2]

Lyon was recruited in 1947 as "Special Assistant to the Chief Medical Director for Atomic Medicine." His charge was to prepare VA to handle claims for injuries associated with the atomic bomb tests. As it turned out, few if any such claims were received, but the Atomic Medicine unit kept up with the literature on radiation effects. Soon, under Lyon's leadership, VA set up a Radioisotope Section of the Research and Education Service, with Lyon as its Chief. Lyon characterized the existence of the "Atomic Medicine" program as a secret, with emphasis on radioisotope research applications in VA serving to divert interest from the nuclear warfare theme.[3] VA became the lead agency for civil preparedness against an atomic attack, and staff of the radioisotope units in the hospitals were responsible for civil preparedness at the local level.[4]

Lyon, who knew key people with the Manhattan Project and the Navy atomic warfare program, used his personal contacts extensively in establishing the new VA radioisotope program. He quickly proceeded to set up radioisotope departments in as many VA hospitals as possible. At each of them, there was a physician chief and a radiation safety officer, generally a physicist with training in nuclear physics. These VA radiation physicists held courses for their communities on atomic preparedness and taught local police and fire departments how to handle Geiger counters. In 1949, the Atomic Medicine program published a *Training Guide for a Course in Radiological Defense*. By the summer of 1950, most VA staff physicians, nurses and dentists, as well as some 400 others, had received this training.[1]

The physicians and scientists in these new VA radioisotope departments began to explore the uses of radioisotopes for diagnosis and treatment. In 1947, the Chief Medical Director established a Central Advisory Committee on Radiobiology and Radioisotopes.
Members of this Committee (Appendix IId and Figure 6.1), who were leaders in the use of radioisotopes in medicine and medical research, advised on all use of radioisotopes by the agency. But the Committee also assisted in establishing the medical research program in general. Three of its members, who were especially close to Dr. Lyon, worked at a practical level to help establish VA radioisotope laboratories in different geographic areas. This Committee was active from 1947 to 1961. It was not until 1955 that a similar advisory committee was appointed with responsibility for other aspects of the VA medical research program.

Figure 6.1. Meeting of the Central Advisory Committee on Radioisotopes
Left to right: Hugh Morgan, M.D.; Perrin H. Long, M.D.; George M. Lyon, M.D.; Admiral Joel Boone, M.D. (CMD), H.L.Friedell, M.D., Ph. D.; Shields Warren, M.D.; A.G.Moseley, Jr, M.D.,. Missing: Stafford Warren, M.D.

The Radioisotope Laboratories

By the end of 1946, sites for six radioisotope laboratories had been identified, primarily based on the presence of staff and consultants who had been involved in the Manhattan Project.[5] The first of these to conduct routine clinical work with radioisotopes (as distinct from research studies) opened at Van Nuys, Calif, in February 1948 with Mortimer E. Morton, M.D., as Chief.[1] Others followed rapidly. By 1949, 12 radioisotope laboratories were functioning; by 1951, there were 14, employing 98 persons; and by the end of 1953, there were 33, with 202 employees. By 1960, 60 such laboratories had been established. In 1965, 86 VA hospitals were licensed under the Atomic

Energy Commission to use radioisotopes; of them, 55 maintained separate Radioisotope Services. In time, these numbers grew so that every VA medical center with an acute-care responsibility provided nuclear medicine services.

Figures 6.2–6.4. 1949 Radioisotope conference in Washington, D.C.

Figure 6.2. Edward D. Hudack, M.D.; Henry Lanz, Raymond Libby, Ph.D.; Bernard Roswit, M.D.; Benedict Cassen, Ph. D.; William W. Saunders, M.D.; Herbert C. Allen, Jr., M.D.; George Meneely, M.D.

Figure 6.3.: Raymond Libby, Ph.D.; Benedict Cassen, Ph.D., Mortimer Morton, M.D., Ph.D; Wallace Armstrong, M.D.; Hymer Friedell, M.D., Ph. D.;George Meneely, M.D., George Lyon, M.D.

Figure 6.4. Benedict Cassen, Ph.D.; Raymond Libby, Ph.D; Joe Meyer, Ph.D.

In 1948, Dr. Lyon convened the first meeting of his Chiefs of Radioisotopes in VA Central Office. These meetings continued twice a year, and later annually, until in the late 1950s they were subsumed in the more general annual VA research meetings (Chapter 3).

Figure 6.5. Harold Weiler, M.D.; George Lyon, M.D. and Graham Moseley, M.D. lead the 1950 Radioisotope Conference

Figure 6.6. Attendees, Fifth Semiannual VA Radioisotope Conference, VAH Framingham, 1950

Dr. Lyon was so eager to set up new radioisotope laboratories that he actively sought out experts in a variety of fields to start them. As a pediatrician, he did not hesitate to recruit fellow pediatricians. The majority of the early VA Chiefs were specialists in internal medicine, however, and this

relatively heavy balance of internists continued in VA nuclear medicine for many years. In VA, the Radioisotope Service in the field hospitals was an independent unit; this encouraged variety and individualism in its Chiefs.

In 1950, Joseph Ross, M.D., at the Framingham (Mass.) VA Hospital, with Herbert Allen, M.D., from Houston, Reginald A. Shipley, M.D., from Cleveland and Leslie Zieve, M.D., from Minneapolis, formed a group to plan a Cooperative Study of Radioiodine Therapy of Hyperthyroidism. Dr. Ross chaired the group and reported its early work at a meeting of VA Chiefs of Radioisotopes held in Central Office in June 1951. A case study protocol was developed for use by all participating radioisotope laboratories. At the next meeting, in Los Angeles in January 1952, the protocol was agreed upon by the participants and the study was launched. Its goals were to determine the relation between dose (in microcuries per gram concentrated by the thyroid) and the outcome of treatment, and to search for characteristics that might predict a patient's response to treatment. The group also proposed to follow patients over the long term to identify any adverse effects of the treatment, especially the development of thyroid cancer.[6] This study, performed on a purely voluntary basis with little urging from Central Office, succeeded in collecting an early body of data, but it failed to reach a definitive conclusion. Some of the Chiefs objected to the degree of standardization required. Even more importantly, Dr. Ross became the founding Associate Dean at the new UCLA School of Medicine in 1954, and after that he lacked time to pursue the study.[7] Nevertheless, this study led to research within VA to improve the thyroid dose estimate for radioiodine.[8, 9] It also set the pace for a more definitive NIH-funded study to address open questions.[10]

While the radioisotope laboratories increasingly concentrated on providing the latest in patient care, they remained at the forefront of nuclear medicine research. At the Wadsworth VA Hospital in Los Angeles in the late 1940s, Dr. Herbert Allen developed a method to map the radioactivity in the thyroid gland by using a directional probe at many points along a grid over the neck.[11]

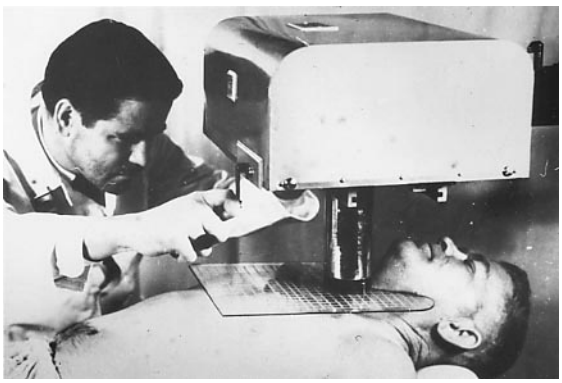


Figure 6.7. Herbert Allen, M.D., manually scans the radioactivity in a patient's thyroid gland

This technique gave crude imaging information and took several hours to complete a study. Allen challenged Benedict Cassen, Ph.D., a physicist at UCLA, to develop an electrically driven scanner. The result was the first nuclear medicine scanner, developed in 1950 by Drs. Cassen, Allen and Goodwin and used to study the thyroids of patients at Wadsworth.[12, 13] At a January 1952 meeting

in Los Angeles, Franz Bauer, M.D.; William E. Goodwin, M.D., and Raymond L. Libby, Ph. D. demonstrated this new device to "mechanically scan" radioiodine in the thyroid gland. This was the beginning of the imaging of radioisotope distribution in intact persons, a technique that has revolutionized the diagnostic and therapeutic approaches to many diseases of various organs.

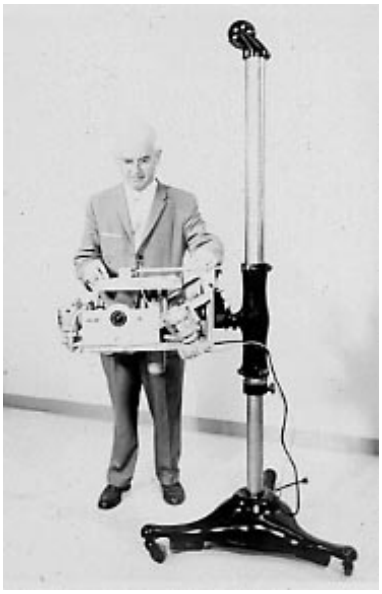


Figure 6.8. Benedict Cassen and the first radionuclide scanner

Later in the 1950s, Manuel Tubis, Ph.D., a radiochemist at Wadsworth, developed a variety of ^{131}I-labeled compounds, of which the most important was iodohippurate (hippuran), a compound that proved very useful in the study of kidney disorders and is still in use.[14, 15]

Figure 6.9. Manual Tubis, Ph.D.

In the late 1950s, Drs. Berson and Yalow at the Bronx VA Hospital announced their radioimmunoassay method (Chapter 11), a discovery that later won a Nobel Prize for Yalow. This technique has revolutionized the measurement of hormones, drugs and body chemicals in tiny samples of blood or tissue.

Local governance

A hospital Radioisotope Committee regulated the activities of the radioisotope laboratories at the local level. Research in these laboratories did not come under the control of the hospital Research and Education Committee until the separate Radioisotope Service in Central Office was dissolved in 1960, making the radioisotope research program a part of Research Service. After that, the hospital's Radioisotope Committee became a subcommittee of the Research and Education Committee, and approval of both of the local committees (Radioisotope and Research and Education) was needed before a research project involving radioisotopes could start. At first, the members of the Radioisotope Committee were exclusively non-VA consultants. Later, the committee also included VA staff experienced in radioisotope use.

By 1962, radioisotope use was widespread in VA (Appendix Va), and patients could be examined through a wide variety of clinical radioisotope studies (Appendix Vb).

Graham Moseley

Shortly after he arrived in VA Central Office, Dr. Lyon recruited A. Graham Moseley, M.D. to join him. Moseley had been on the chemistry faculty at Marshall University before World War II. During the war, he was in the Navy and was present with Lyon at the Bikini tests. At Bikini, he is reported to have detected high levels of ^{24}Na in a ship's onboard distiller, used to prepare drinking water from sea water.

When Lyon became ACMD/R&E in 1952, he appointed Moseley to be Chief of the Radioisotope Program, which became a separate service when Research and Education became a recognized independent Office in 1953. Moseley continued to administer the program until he retired in 1967. He had an intimate knowledge of all of the radioisotope laboratories, and he used his considerable talents and knowledge of the "system" to expand the radioisotope program. He is remembered as "a delightful guy who ran the program and tried to give everyone what he needed to do a good job."[16]

Figure 6.10. A. Graham Moseley

Figure 6.11. Moseley and Harold Weiler at a planning meeting

When Ralph Casteel left Research and Education to become Special Assistant to the Chief Medical Director in 1956, Dr. Lyon assigned Moseley the additional duties of his "Special Assistant." Moseley continued as both Special Assistant to the ACMD/R&E and head of the Radioisotope Program until 1965, when Benjamin Wells, then the ACMD/R&E, arranged to have Moseley and the radioisotope program transferred out of the Research and Education Office and into the Professional Services Office.[18] Moseley's duties as Special Assistant to the ACMD/R&E were turned over to a new Deputy ACMD, James A. Halsted, M.D. This was the official beginning of the Nuclear Medicine Service in VA Central Office as a clinical entity, with Moseley as its Director.

At that time, Moseley wrote to all of the Radioisotope Services asking for material to include in a brochure he intended to write about the radioisotope research program. The brochure itself seems to have disappeared, if it was ever completed, but many of the responses are still available. They paint a picture of a group of contented, productive, hospital-based clinicians and scientists, spending much of their effort on patient-oriented research but also conducting many types of bench research and establishing a rapidly increasing number of patient-care procedures. Their research contributed to many disciplinary areas that use the tracer principle, which was invented in 1912 and is based on the principle that radioactive elements have identical chemical properties to their nonradioactive form and therefore can be used to trace chemical behavior in solutions or in the body.[19]

Richard Ogburn, Belton Burrows and Gerald Hine

When Graham Moseley retired in 1967, his position as Director of the Central Office Radioisotope Service was filled by Richard Ogburn, M.D., who had been Chief, Radioisotopes, at the Omaha VA Hospital and had set up the first hospital-based nuclear reactor in addition to running an active clinical and research program. But Ogburn died shortly after he was appointed.

Figure 6.12. Richard Ogburn, M.D.

Figure 6.13. The TRIGA reactor at the Omaha VAMC

After Ogburn's death, the Director position remained vacant. Concerned about this lack of leadership, four Nuclear Medicine Chiefs, William Blahd, M.D. from Los Angeles, Ervin Kaplan, M.D. from Hines (Ill.), Richard Peterson, M.D. from Iowa City and Belton Burrows, M.D. from Boston, met with Lyndon Lee, M.D. the Associate Chief Medical Director for Professional Services. They offered to take over the program on an interim basis in rotation. Burrows (Figure 6.6) received the first month's assignment. At the end of that month, the others persuaded him to

continue. However, Burrows did not want to move to Washington or to give up his program in Boston. So for the next five years, he commuted between Boston and Washington, managing the national clinical nuclear medicine program as well as the nuclear medicine programs at his hospital and at Boston University.[16, 20, 21] However, he was responsible only for the clinical Nuclear Medicine Service and not for leading research in the field, still the purview of Research Service. In 1969, Gerald Hine, Ph.D., a physicist who had worked with Burrows at Boston and then for the International Atomic Energy Commission, came to the Central Office Research Service as Program Chief for Radioisotope Research.[22]

Figure 6.14 Gerald Hine, Ph.D.

The place of nuclear medicine within VA

Over the years, nuclear medicine in VA has experienced a number of organizational changes. Although it started as a Section of the Atomic Medicine Division within the Research and Education Service, it also originally enjoyed a direct line to the Chief Medical Director. In 1953, when the Research and Education Service was elevated to a freestanding Office, it contained three Services: Atomic Medicine, Research and Education. In 1960, the Atomic Medicine Service (which was active only through its Radioisotope Section) was abolished, and the radioisotope research program was incorporated within Research Service.

Increasingly, with maturation of the field, more and more of the radioisotope work at VA hospitals became established patient care procedures rather than pure research. Some clinical funding of the hospital-based program began in 1955. In 1965, as previously mentioned, a clinical Nuclear Medicine Service was officially founded within Professional Services in VACO, though the hospital Radioisotope Services were still considered to be primarily research. Finally, in about 1971, when Mark J. Musser, M.D., was Chief Medical Director, Nuclear Medicine became a clinical service at VA hospitals, with support of patient-care activities coming from clinical funds rather than research funds. By 1972, when James J. Smith, M.D., became Director of Nuclear Medicine in Central Office, the clinical Nuclear Medicine Service had become entirely independent of the Research Service.

Basic scientists in the Radioisotope Services

The physicists and other basic scientists recruited into the early radioisotope program served as a nucleus for later development of a corps of basic scientists for the VA research program as a whole. Stemming from their importance to the “atomic medicine” program, the nuclear medicine scientists

commanded high salary grades, and this soon led to upgrading of all basic scientist positions in VA research.[4] Among the nonclinician scientists who started their VA work in the radioisotope program of the 1940s, 1950s and 1960s were Rosalyn Yalow, Ph.D. at the Bronx, who won the Nobel Prize; Joe Meyer, Ph.D., later VACO Program Chief in Basic Sciences; David Cohn, Ph.D. later ACOS for Research and Development at Kansas City; Gerald Hine, Ph.D. at Boston; Joseph Rabinowitz, Ph. D. at Philadelphia; Helmut Gutman, M.D. at Minneapolis; Charles C. Irving at Memphis; Raymond Lindsay at Birmingham; and Manuel Tubis, Ph. D, Nome Baker, Ph. D., and Michael Shatz at Wadsworth.

Nuclear medicine as a physician specialty

In 1955, the Society of Nuclear Medicine was founded by a small group of physicians and scientists, including Rex Huff, M.D., Chief of Radioisotopes at the Seattle VA Hospital. Huff gave the first paper in the scientific session of the Society's first meeting, "Estimates of Cardiac Output by In Vivo Counting of I^{131} Labeled HSA." VA nuclear medicine physicians and scientists have been prominent in the Society of Nuclear Medicine ever since.

Figure 6.15. Rex Huff, M.D.

In 1969, nuclear medicine was one of the subject areas in which VA's new Research and Education Training Program (Chapter 14) was established, with a distinguished selection committee.[22] Six of these formal training programs were in place in 1970, and their numbers grew over the next two years. These programs, funded by research money but administered by the Education Service, were designed to train physician trainees with at least two years of prior residency training in a related field in both the patient care and the research aspects of nuclear medicine. The intent was to provide an entry opportunity for physicians who wanted to enter academic nuclear medicine. This program arrived at an opportune moment for the field of nuclear medicine, which at that time had no specialty board and no formal residency programs. In the Nuclear Medicine Training Programs, young physicians learned both clinical and research skills. Many remained in VA, enriching the program's research and clinical components. In 1972, this program was folded into VA's regular residency program, and residency slots were added to hospitals' allocations to replace the lost trainee slots. In this way, VA developed nuclear medicine residency programs well before most other institutions supported them.

The physicians who entered the early VA radioisotope program have been among the pioneers in nuclear medicine. Among the many physicians who contributed to the program in the 1950s and early 1960s and emerged as leaders in nuclear medicine practice and research were Drs. Solomon Berson, William Blahd, James Pittman, Leslie Zieve, Ervin Kaplan, Marcus Rothschild, Belton Burrows, Ralph Cavalieri, Robert Donati, Clayton Rich, Lindy Kumagai, Richard Spencer, Ralph Gorton, Gerald Denardo, David Baylink, Walter Whitcomb, Robert Meade, Francis Zacharewich, Leo Oliner and Robert Chodos. All of these physicians have made important contributions to medicine and medical science.

In 1972, the American Board of Nuclear Medicine gave its first certifying examination for physician specialists. At about the same time, access to nuclear medicine services became a requirement for hospital certification. The specialty of nuclear medicine had matured. It was now in the mainstream of American medicine. Within VA, Nuclear Medicine Services took their place next to the other clinical services.

Today, the primary job of a VA nuclear medicine physician is patient care. Many of them continue to be active in research, but their research is now under the same umbrella as that of other VA research investigators. Those who recall the early days take pride in VA as the birthplace of their specialty.

References

1. Lyon, G.W. "VA radioisotope program: Historical." *25th meeting of the Committee on Veterans Medical Problems*. Washington, DC: National Academy of Sciences, 1952, 553-554.

2. Interview with Clo Gooding, May 2, 1988 at VA Central Office, Washington, DC.

3. Lyon, G.W. "VA radioisotope program: General statement of objectives and principles." *25th meeting of the Committee on Veterans Medical Problems*. Washington, DC: National Academy of Sciences, 1952, 554-556.

4. Interview with Joe Meyer, Ph.D., May 4, 1992 at Dr. Meyer's home in suburban Maryland.

5. Interview with Herbert Allen, M.D., January 28, 1994 at Dr. Allen's office in Houston, TX.

6. Ross, J. "Cooperative study of radioiodine therapy for hyperthyroidism." *25th meeting of the Committee on Veterans Medical Problems*. December 5, 1952. Washington, DC: National Academy of Sciences, 1952, 576-578.

7. Telephone interview with Joseph Ross, M.D., February 1, 1990.

8. Goodwin, W.E., Cassen, B. and Bauer, F.K., "Thyroid gland weight determination from thyroid scintigrams with postmortem verification." *Radiology*, 1953. **61**: 88-92.

9. Bauer, F.K. and Blahd, W.H., "Treatment of hyperthyroidism with individually calculated doses of 131I." *Arch Intern Med*, 1957. **99**: 194-201.

10. Dobyns, B.M., Sheline, G.E., Workman, J.B., Tompkins, E.A., McConahey, W.M. and Becker, D.V., "Malignant and benign neoplasms of the thyroid in patients treated for hyperthyroidism: A report of the cooperative thyrotoxicosis therapy follow-up study." *J Clin Endocrinol Metab*, 1974. **38**: 976-998.

11. Allen, H.C., Libby, R. and Cassen, B., "The scintillation counter in clinical studies of human thyroid physiology using I131." *J Clin Endocrinol Metab*, 1951. **11**: 492-511.

12. Cassen, B., Curtis, L., Reed, C. and Libby, R., "Instrumentation for I131 use in medical studies." *Nucleonics*, 1951. **9**: 46-50.

13. Bauer, F.K., Goodwin, W.E., Libby, R. and Cassen, B., "Visual delineation of thyroid glands in vivo." *J Lab Clin Med*, 1952. **39**: 153-158.

14. Tubis, M., Posnick, E. and Nordyke, R.A., "Preparation and use of I131 labeled sodium iodohippurate in kidney function tests." *Proc Soc Exp Biol Med*, 1960. **103**: 497-498.

15. Nordyke, R.A., Tubis, M. and Blahd, W.H., "Use of radioiodinated hippuran for individual kidney function tests." *J Lab Clin Med*, 1960. **56**: 438-445.

16. Interview with William Blahd, M.D., November 8, 1991 at Dr. Blahd's office in the VA Medical Center, Los Angeles, CA.

17. Telephone interview with James Pittman, M.D., March 13, 1988.

18. Interview with Ralph Casteel, May 3, 1988 at a restaurant in Bethesda, MD.

19. Letters from Radioisotope Service Chiefs, collected by Clo Gooding., written in 1965 to A. Graham Moseley, Jr.

20. Interview with Ervin Kaplan, M.D., May 1, 1994 at Dr. Kaplan’s home in Wilmette, IL.

21. Interview with Belton Burrows, M.D., October 27, 1992 at Dr. Burrows's home in Brookline, MA.

22. *Medical Research in the Veterans Administration, FY 1969*. Washington, DC: Government Printing Office, 1969, ix.

(Intentionally Blank)

Section III. The VA Research Program Takes Off 1954-1959

(Intentionally Blank)

Chapter 7. The Intramural Research Program, 1954-1959

Research becomes a Service

In 1953, the Research and Education Service in the young VA Department of Medicine and Surgery (DM&S) was upgraded in status, becoming the new Research and Education Office with three Services: Research, Education and Atomic Medicine. George M. Lyon, M.D., the Assistant Chief Medical Director (ACMD) for Research and Education succeeding Dr. Harvey Cushing, headed the new Office[1] but did not give up his title of Director, Atomic Medicine Service. Although Dr. Graham Moseley actually ran the radioisotope program, Lyon continued his intense interest and, some felt, favored it over Research and Education.[2] John C. Nunemaker, M.D., was a very active Director of the Education Service after serving as Acting Chief, Research Section, in 1952[3] when Alfred Lawton left.

Figure 7.1. John Nunemaker, M.D.

Figure 7.2. Martin Cummings, M.D.

Martin M. Cummings, M.D., becomes Director, Research Service

Shortly after the new Research Service was created, Martin M. Cummings, M.D., became its Director. Cummings had worked at the Tuberculosis Evaluation Center in Atlanta (part of the U.S. Public Health Service's Centers for Disease Control) from 1947 to 1950. Drs. Magnuson and Barnwell, after visiting Dr. Cummings in his laboratories, persuaded him to move to the Atlanta VA Hospital in 1950 to start a tuberculosis research laboratory and take over care of tuberculosis patients. In 1954, they recruited him to VA Central Office.[4]

Research Service, 1954

When Cummings arrived in Central Office, his professional staff consisted of only three people. Harold Weiler (Figure 6.11), a former high school science teacher, was "Chief, Research Laboratories," and worked on plans for building and equipping general medical research

laboratories. Cummings recalled that, during his time at Research Service, a large fraction of the contract budget went for prosthetics research. Marjorie Wilson, M.D., "Chief of Contracts Research," left soon after Cummings's arrival and was succeeded by T. S. Moise, M.D. The third staff member, Graham Moseley, worked closely with Cummings even though he was not officially in the Research Service.

Research space remained a big issue. There was little point in increasing the budget for studies unless intramural physicians and scientists had space to do their work. By this time, some research space was included in plans for new hospitals, and a great deal of effort went into preparing these plans. Cummings remembered this as a difficult but rewarding process, in which his initial plans usually ended up being significantly reduced by VA's own construction design section, as well as by review staff at the Bureau of the Budget. In some instances, he recalled, space for research was provided through a patchwork approach:

> "I remember the VA Hospital in Durham because the faculty at Duke was real gung-ho. They wanted to do a lot of work in the VA. After our construction plans had been trimmed way back, they put up a Quonset hut adjoining the VA and made that a research facility. A lot of the medical schools contributed a lot of space as well. I don't claim to have had any intimate influence on a design but I always fought for a strategic location and I fought for an adequate square footage."[4]

As a result of the efforts of Weiler and Nunemaker (while Nunemaker was responsible for Research)[5], Research Service could soon offer generic plans for laboratory renovation and lists of equipment for setting up new laboratories. To save money and paperwork, Central Office bought some frequently needed equipment in volume for distribution to laboratories. Cummings, Weiler and Moseley worked together to design both medical research and radioisotope laboratories.[4]

Research program reaches out

Cummings worked hard to improve VA affiliations with medical schools. For example, he rapidly opened negotiations with the new UCLA medical school, which lacked research laboratories for arriving faculty. Renovations at Wadsworth VA Hospital provided laboratories for these faculty members. Admiral Boone, the CMD, and Stafford Warren, the UCLA Dean, reached an informal agreement that Cummings carried out.[4] VA paid for setting up the laboratories but thereafter made very little financial contribution to the UCLA faculty programs using the labs. However, the presence of faculty members, working side by side with VA investigators, enriched Wadsworth's research program. Even after the UCLA Medical Center, which included faculty laboratories, opened in 1955, several full-time UCLA faculty members remained at Wadsworth. Meanwhile, as the intramural program at Wadsworth grew, it took over space developed for UCLA. A highly productive medical research program followed.

NIH grants become available to VA investigators

During a visit to Los Angeles to help implement the UCLA affiliation, Cummings talked with Samuel Bassett, M.D., a VA physician and investigator also on the UCLA faculty. Bassett complained that VA investigators were not allowed to compete for NIH funds. Shortly after that

visit, Cummings talked with Ernest Allen, the Associate Director of the Division of Research Grants at NIH. Allen told him that NIH had been receiving applications from VA investigators but had turned them all down administratively, owing to a lack of a funding precedent. After Cummings raised the issue, Allen looked into the policy history and checked the legal language. He found nothing in the law to forbid NIH from funding principal investigators from VA. Shortly thereafter, Cummings and Allen went together to Philadelphia for an NIH site visit. They discussed the matter further and on the return trip drafted an agreement to allow VA to compete for NIH funds through their affiliated universities.[4] Allen proceeded to make the change in policy at NIH. The new availability of research funding, which Cummings later described as a major incentive for recruitment and retention of VA physicians and scientists, was announced within VA in January 1954.[7]

Promoting VA research

When Dr. John Barnwell, who had spearheaded the tuberculosis trials (Chapter 5) became ACMD in 1956, he conceptually broadened the scope of the research program. It was natural that the tuberculosis studies grew more closely identified with Research Service during his period of Research and Education leadership. He encouraged interaction between his staff and other research leaders in VACO.

Barnwell was a good critical observer of research, even though he himself was not very active in research except for his interest in the tuberculosis cooperative studies. Barnwell was a humanist and philosopher. He remained current in his field and was also personally generous.[4]

Barnwell's predecessor, Dr. George Lyon, had taken a rather conservative approach toward seeking VA research support from outside the agency. In contrast, Barnwell encouraged Cummings to "do anything honorable to improve the budget." Barnwell, as well as Dr. William S. Middleton, who became Chief Medical Director in 1955, worked with members of Congress and professional organizations toward this goal. Cummings and Barnwell made contact with Mary Lasker and Florence Mahoney, two remarkable women who were well known at their time for their influential advocacy in Congress for health care research funding. These influential research advocates arranged for meetings with Senator Lister Hill, Chairman of the Appropriations Committee, and other members of Congress who became interested in the VA research program.

Another strong supporter of VA research who was particularly influential with the Congress was prominent Houston surgeon Michael DeBakey, M.D., who had been active on the Committee for Veterans Medical Problems since its inception. DeBakey recalled that "in those early days, I was there every year testifying both in the House and the Senate for their appropriations for research and emphasizing… this was the way to advance the quality of care in VA—by putting in research and having these committee affiliations with medical schools as an integral part of that activity."[8]

William Middleton, M.D.

William S. Middleton, M.D., the Chief Medical Director from 1955 to 1963, was a strong advocate for the VA research program. Middleton had been Dean of the University of Wisconsin School of Medicine since 1935. He had pushed the concept of VA-medical school affiliation since the

beginning of DM&S, and affiliations flourished during his term as Chief Medical Director. He viewed his role as physician leader. Each week while he was in Central Office, Middleton made clinical rounds at the Washington, D.C., VA Hospital. He was a taskmaster— respected by all, loved by many and feared by some. He furthered the research program in any way he could, and his support was critical to the program's growth spurt during his years as Chief Medical Director.

Cummings called Middleton "the most extraordinary administrator that I ever met in the VA. If you were ever invited to travel with him and go to the field, he would do his duty and perform the necessary business with the hospital director and all of the staff, but you'd never get out of a VA hospital without making rounds with him and seeing patients. And he taught me a lot of medicine while we were both in an administrative job."[4]

Figure 7.3. William S. Middleton, M.D.

While he was in Central Office, Cummings ran a personal research laboratory and saw patients at Mt. Alto (Washington, DC) VA Hospital. He was also on the faculty of George Washington University Medical School and lectured there. But he spent more time at his Mt. Alto laboratory, where he was assisted by two technicians and a postdoctoral fellow in a study of sarcoidosis. Both Barnwell and Middleton encouraged these academic activities.

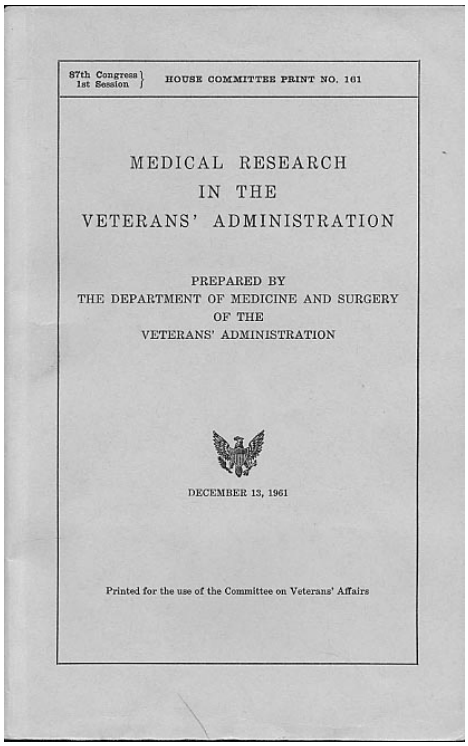
VA medical research becomes law

In 1955, Congress appropriated an explicit VA research budget for the first time. But, in dealings with Congress, Cummings discovered that a lack of legal authorization for research within VA was a major impediment to improving the research budget. Middleton agreed to Cummings's efforts seeking legal authorization. The political dealings were successful. In September 1958, with passage of Title 38, USC, section 4101, the words "including medical research" were added to the legal definition of the mission of the DM&S.[9] This helped to justify increased funding for VA medical research.

Medical Research in the Veterans Administration

As a part of their efforts to educate Congress, Drs. Barnwell, Cummings and Nunemaker, with

encouragement from Dr. Middleton, prepared *Medical Research in the Veterans Administration*, the first annual report to Congress on VA's research program. This first report, presenting material from fiscal year 1956, was published on March 5, 1957.[10] In his transmittal letter Dr. Middleton said, "The compelling force to accelerate medical research within the Veterans' Administration has been tempered only by difficulties in engaging qualified medical staff and in achieving the necessary expansion of laboratory space and related physical facilities." *Medical Research in the Veterans Administration* continued through 1975 as an annual report, describing all aspects of the VA medical research program, including research supported by patient care services and the Follow-up Agency. An annual "supplement" detailed individual research projects.


87th Congress
1st Session
HOUSE COMMITTEE PRINT NO. 161

MEDICAL RESEARCH
IN THE
VETERANS' ADMINISTRATION

PREPARED BY
THE DEPARTMENT OF MEDICINE AND SURGERY
OF THE
VETERANS' ADMINISTRATION

DECEMBER 13, 1961

Printed for the use of the Committee on Veterans' Affairs

Figure 7.4. VA's annual report to Congress on its research program

This report had evolved from a simple catalog inventory of research projects. When Middleton took Cummings on visits to hospitals, he would complain, "We don't have anything like the NIH Inventory of Research Projects." Cummings set out to create such an inventory. Marjorie Wilson, who returned to Central Office in 1956 as Assistant Director, Education Service, under John Nunemaker, worked with Cummings on this effort. They received important help from Marguerite Duran of Medical Records, who indexed and classified the research projects. In 1956, this catalog contained over 3,600 projects—a number that had increased to 5,000 by the time Cummings left Central Office in 1959. Cummings took this catalog with him whenever he went to Capitol Hill and used it as ammunition to show members of Congress that VA was conducting excellent research work.[4]

Beginnings of the Career Development Program

The VA Research Career Development Program, which received high acclaim through the years as a source of physician leadership in VA and academia, began in 1956 with the Clinical Investigator Program. Drs. Cummings and Nunemaker, encouraged by Dr. Middleton, initiated the concept of providing young physicians with VA appointments to concentrate on research.[4]

When Marjorie Wilson returned to VA Central Office, her major task was to organize the Clinical Investigator program. In preparation, she reviewed programs of the NIH, the American Heart Association and other organizations and established a formal system of applications and an evaluation committee. The "Selection Committee for Clinical Investigators," forerunner of the long-standing Research Career Development Committee, was established in November 1956. Its founding members were J. Burns Amberson, M.D., from New York's Bellevue Hospital; Stanley E. Dorst, M.D., Dean, University of Cincinnati School of Medicine; Maxwell Finland, M.D., from Harvard Medical School; Carl A. Moyer, M.D., from Washington University, St. Louis; and Harold G. Wolff, M.D., from Cornell. From its inception, this committee upheld high selection standards.[11] From the very first group, the selectees made major contributions to academic medicine and the VA medical program.[12]

Wilson also started the Senior Medical Investigator program in 1959, modeled on programs for senior scientists such as the American Heart Association Established Investigator program. The Selection Committee for Clinical Investigators also reviewed the Senior Medical Investigators, but Central Office leadership played an active role in their selection. Oscar Auerbach, M.D., Ludwig Gross, M.D. and Edward D. Freis, M.D. [13-15] among the earliest appointees, all recalled in interviews that they first heard of the program when they received calls from Dr. Middleton or Dr. Cummings inviting them to accept the appointment. Senior Medical Investigators could work independently on research of their choosing. They were permitted to accept teaching and patient care responsibilities, but their primary effort was on research. As with the Clinical Investigators, Senior Medical Investigators were supported directly from research funds.

New Central Office research staff

Charles Chapple, M.D., came to the Central Office Research Service in 1956 as Chief of Clinical Studies (cooperative studies). Chapple, a pediatrician friend of Dr. Lyon, had previously been at Children's Hospital in Philadelphia and was Professor of Pediatrics at the University of Pennsylvania. He had been honored by election to the "Young Turks" and held several consultantships. In addition, Chapple was an accomplished amateur archeologist and botanist. While in the Navy in the Aleutians, he had discovered three new plant species, one named after him. He invented the Isolette infant incubator and a humidification device, which led to the Croupette.[4]

Figure 7.5 Charles Chapple, M.D.

Around 1958, Chapple took on special responsibility for furthering research in aging. An Advisory Committee on Problems of Aging was established in December 1955, with rotating membership of five leaders in the field. This Committee assisted Chapple in encouraging research relevant to aging, a problem of special interest to Chief Medical Director Middleton. Abraham Dury, Ph.D., who served on this Committee in the early 1960s, recalled that meetings dealt primarily with policy and strategic issues and did not review the science of ongoing projects.[16]

W. Edward Chamberlain, M.D., came to VA Central Office in 1957 as "Special Assistant to the CMD for Atomic Medicine," apparently recruited by Dr. Lyon to be his successor.[17] A radiologist, Dr. Chamberlain had been Professor of Radiology at Temple University Medical School. He served on the Committee on Veterans Medical Problems from 1956 to 1958. From 1958 to 1960, Chamberlain's title was "Assistant Director (Plans), Research Service." In 1960, he received the Longstreth Medal from the Franklin Institute in Philadelphia for his earlier innovative contributions to radiology.[18]

The Research Advisory Committee

By the 1950s, the Committee on Veterans Medical Problems (Chapter 4) had become less active in advising the VA intramural research program. To fill this gap, in September 1955, six months after William S. Middleton became Chief Medical Director, VA appointed its own Advisory Committee on Research. This Committee (Appendix IIe) continued to be active until 1960, when it was reconstituted. It reviewed the research program and advised about new directions. Generally, a new program such as the Clinical Investigator program would be reviewed and approved by this Committee before implementation. At times, especially in the early years, members met at individual hospitals to review the local research program. However, they did not review individual research projects.[2]

Annual Research Conference

The annual research conferences, started by Dr. Cushing at the Atlanta meeting in January 1952 (Chapter 3), continued to be well attended and popular. Invited were all Associate Chiefs of Staff for Research and Education (ACOS/R&D)'s, Chiefs of the Radioisotope Services, Clinical Investigators and Senior Medical Investigators, as well as other VA research scientists whose papers were accepted for presentation.

The second Annual Research Conference was held at the Houston VA Hospital, and the next seven at the Memphis VA Hospital. By the December 1959 10th conference, the group was too large to meet in a VA facility and began meeting for the next eight years at the Netherlands Hilton Hotel in Cincinnati. By 1959, the Annual Research Conference required two concurrent sessions for presentation of 108 papers chosen from 288 submitted abstracts.[19]

At the 1959 conference, attendees established a Middleton Award for research accomplishment to recognize the importance of Dr. Middleton's support for the research program. "The managers of VA installations" were to nominate recipients, and a special committee with representatives from both the field and Central Office was to make the selection. The Middleton Award "is considered the highest honor that can be given by colleagues in recognition of outstanding quality in research."[20] Solomon A. Berson and Rosalyn S. Yalow, who later were awarded the Nobel Prize, received the first Middleton award the following year at the annual research conference. The award is still given annually, and its recipients (Appendix I) reflect the spectrum of VA medical research.

Growth of the Cooperative Studies Program

More and more VA physicians began to recognize VA's potential as a site for cooperative clinical trials. By 1956, the studies on chemotherapy of tuberculosis (Chapter 5) had expanded to include studies of other pulmonary diseases and an intensive collaborative effort to develop and standardize pulmonary function tests. These studies were extended to include coccidioidomycosis and histoplasmosis. Fifty-four VA and four military hospitals collaborated in these studies, and their reports were distributed to 35 foreign countries as well as throughout the United States. As a separate effort, eight VA hospitals collaborated in a study of possible effects of tranquilizing drugs on tuberculosis patients who were also psychotic.[21]

A study of the new antihypertensive drugs began in eight VA hospitals.[22] This study (Chapter 9), later brought VA wide recognition and won Dr. Freis the Lasker Award and a nomination for the Nobel Prize.

A new study of therapies for esophageal varices[23] compared medical methods to surgical procedures. This study group continued into the mid 1970s, comparing long-term results in patients who underwent portacaval shunts with a control group treated medically. The procedure was found to have no survival or lifestyle benefit,[24] but the study showed that portacaval shunt did decrease the hematological problems of hypersplenism.[25]

At the end of 1956, plans included cooperative studies on resistant staphylococcal infections, sarcoidosis and treatment of coronary artery disease.[26] Several cooperative studies on cancer chemotherapy were in progress.[27] The number of active studies grew rapidly; the fiscal year 1960 annual report listed 34.[28]

By 1959, the VA cooperative studies on chemotherapy of psychiatric disorders (Chapter 8) were well under way. The independent cooperative study of patients diagnosed with psychosis and tuberculosis disbanded, reporting essentially negative findings: the combination of anti-tuberculosis drugs and various tranquilizers was not harmful and isoniazide, even in high doses, had no adverse effect on psychiatric status of patients in need of mental hospital care. Electric shock therapy

combined with anti-tuberculosis drugs was found not to cause untoward complications, and management of these patients' disease on full activity without bed rest was effective. Therapeutic results for the patients' tuberculosis were very good, and the full activity program was believed valuable in management of the psychiatric condition. Annual chest x-rays for all patients in neuropsychiatric hospitals, with immediate isolation of actual or suspected tuberculosis cases, resulted in a marked decline in new cases. A randomized study of isoniazide administration to such patients was planned but not put into effect because of the small number of newly discovered cases.

Early cooperative clinical trials (Table 7.1) tended to share some structural characteristics. One or more biostatisticians would be involved. Often the trials were based in Central Office, but university and other biostatisticians also participated. There was a board of consultants and a Central Office-based coordinator, most frequently a physician in one of the professional services. For example, Edward Dunner, M.D., who later joined Research Service but who was at that time a member of the Tuberculosis Service, coordinated the studies on antihypertensive agents, diabetes mellitus and other endocrine diseases, and the pulmonary disease studies, outgrowths of the tuberculosis trials. Lyndon E. Lee Jr., M.D., at that time a member of Surgery Service, coordinated all 10 of the VA-funded cooperative surgery studies, as well as those funded by the National Cancer Institute. In 1956, 11 Eastern VA hospitals and five in the West participated in two regional cancer chemotherapy cooperative studies. These NCI-funded studies involved both VA and university hospitals. In addition, several NCI-funded projects based entirely within VA continued for many years. These included VA study groups for cancer chemotherapy, lung cancer and surgical adjuvant cancer chemotherapy.

The endocrine disorders cooperative study did not produce the clinical answers desired but nevertheless made an important contribution. The original plan was to study adrenal insufficiency and other rare diseases, taking advantage of the huge VA-wide patient population for a more robust number set. To prepare for the clinical study, five steroid assay laboratories were established in

Table 7.1. VA cooperative study groups active during the 1950s

Study	Years active
Chemotherapy of tuberculosis	1946-1974
Prefrontal lobotomy	1950-1956
Multiple sclerosis	1954-1963
Sarcoidosis	1954-1956
Pulmonary function testing	1954-1965
Antihypertensive drugs	1956-1975
VA cancer chemotherapy group	1956-1968
Western cancer chemotherapy group	1956-1964
Southwestern cancer chemotherapy group	1956-1964
Esophageal varices	1956-1975
Peptic ulcer surgery	1956-1972
Ruptured intervertebral disk	1956-1967
Surgery of Parkinsonism	1956-1968
Hospital infections	1956-1963
Coccidioidomycosis	1957-1961
Histoplasmosis	1957-1965
Blastomycosis	1957-1965
Tuberculosis in psychotic patients	1957-1959
Atherosclerosis	1957-1972
Lung cancer	1957-1975
Adjuvant Cancer Chemotherapy	1957-1975

Surgery of solitary pulmonary nodules	1957-1968
Lung cancer diagnosis	1957-1962
Surgery of coronary artery disease	1957-1975
Evaluation of analgesics	1957-1962
Chemotherapy in psychiatry	1957-1973
Psychology research	1957-1962
Diabetes mellitus	1958-1965
Endocrine disorders	1958-1966
University surgical adjuvant study	1958-1963
Early diagnosis of lung cancer – pilot	1958-1963
Outpatient psychiatry	1958-1964
Atrophic lateral sclerosis – assisting NINDB	1958-1961
Functional deafness	1958-1961
Gastroenterology (gastric ulcer)	1959 -1969
VA Prostate Cancer Chemotherapy Study Group	1959-1963
Midwestern cancer chemotherapy group	1959-1964

medical centers. These laboratories developed standardized chemical procedures for assay of plasma 17-hydroxycorticosteriods and standardized the test for ACTH stimulation.[29] While the study never accrued enough patients to provide definitive results about Addison's disease, the reference laboratories' important work set standards for steroid hormone assays that were widely adopted.

Special Laboratories

In some cases, when a research project was judged to need centralized administration, it was formally established as a "Special Laboratory." The first of these, a laboratory at the Boston VA Hospital charged with the study of epilepsy, started in 1952; others followed quickly. These laboratories were specially funded from and reported directly to Central Office, in contrast with other research projects, which were controlled and funded through the hospital's Research and Education Committee. This seems to have been a transitional mechanism, brought into play when the concept of a hospital's intramural research program as a single "laboratory" seemed inappropriate. As hospital-based programs diversified and formal funding mechanisms were put in place, the Special Laboratories were no longer necessary. A number of the most productive leaders of the laboratories (Appendix VI) became medical investigators or senior medical investigators (Chapter 14). By 1970, almost all of the Special Laboratories had been closed or absorbed into other programs

Examples of research by individual staff members at VA hospitals

By the close of the 1950s, the VA research program was still youthful, growing and very much decentralized. Any VA staff member who wanted to conduct research generally could, though very likely on his or her own time. There was still room, in VA and elsewhere, for a physician untrained in research to learn how to conduct research and to carry out the work. Some of this work proved to be important. The atmosphere encouraged innovation, but systems were not yet in place to discourage mediocrity. The result was a varied program that centered on clinical issues.

Many important VA research programs began during the 1950s. Among them: the development of radioimmunoassay by Berson, Yalow and their colleagues at the Bronx VA Hospital (Chapter 11); the studies led by Edward Freis at the Washington VA Hospital that eventually proved the

importance of pharmacotherapy of hypertension (Chapter 9); Oscar Auerbach's studies at the East Orange (N.J.) VA Hospital proving that smoking causes lung cancer (Chapter 10); and the studies led from the Central Neuropsychiatric Research Laboratory at Perry Point (Md.) VA Hospital that proved the efficacy of antipsychotic drugs (Chapter 8).

Following is a brief sampling of other VA intramural research programs in progress during the 1950s:

Dallas–Diabetes

When Roger Unger, M.D., arrived at the Dallas VA hospital in 1956, he found that Seymour Eisenberg, M.D., Leonard Madison, M.D., and Willis Sensenbach, M.D. were collaborating on studies of cerebral blood flow, using the Kety method in a variety of clinical conditions. Among other findings, they showed that cerebral blood flow in confused cardiac patients is markedly reduced.[30] Unger, who had been hired as a clinician, had little time for research, but Eisenberg nonetheless gave him a corner of the laboratory for research.

Noting he had never had any specific training in doing research, Unger credited two technicians in the radioisotope laboratory, Mary McCall and Ann Eisentraut with getting him started.

> "They were dying to do research, but they didn't know how to apply their skills. I had a lot of ideas but few skills. So we were able to work together. They were tremendously helpful."[31]

After a new Chief of Medicine freed some of Unger's time for research, he began his long and distinguished career as a diabetes researcher. He collaborated with Madison on a series of studies on the metabolic effects of insulin and of tolbutamide[32-37] and on a tolbutamide test for mild diabetes.[38, 39]

Figure 7.6 Roger Unger, M.D.

Unger's most important early contribution to diabetes research was developing, with his colleagues, a practical assay to measure glucagon. As he described this effort:

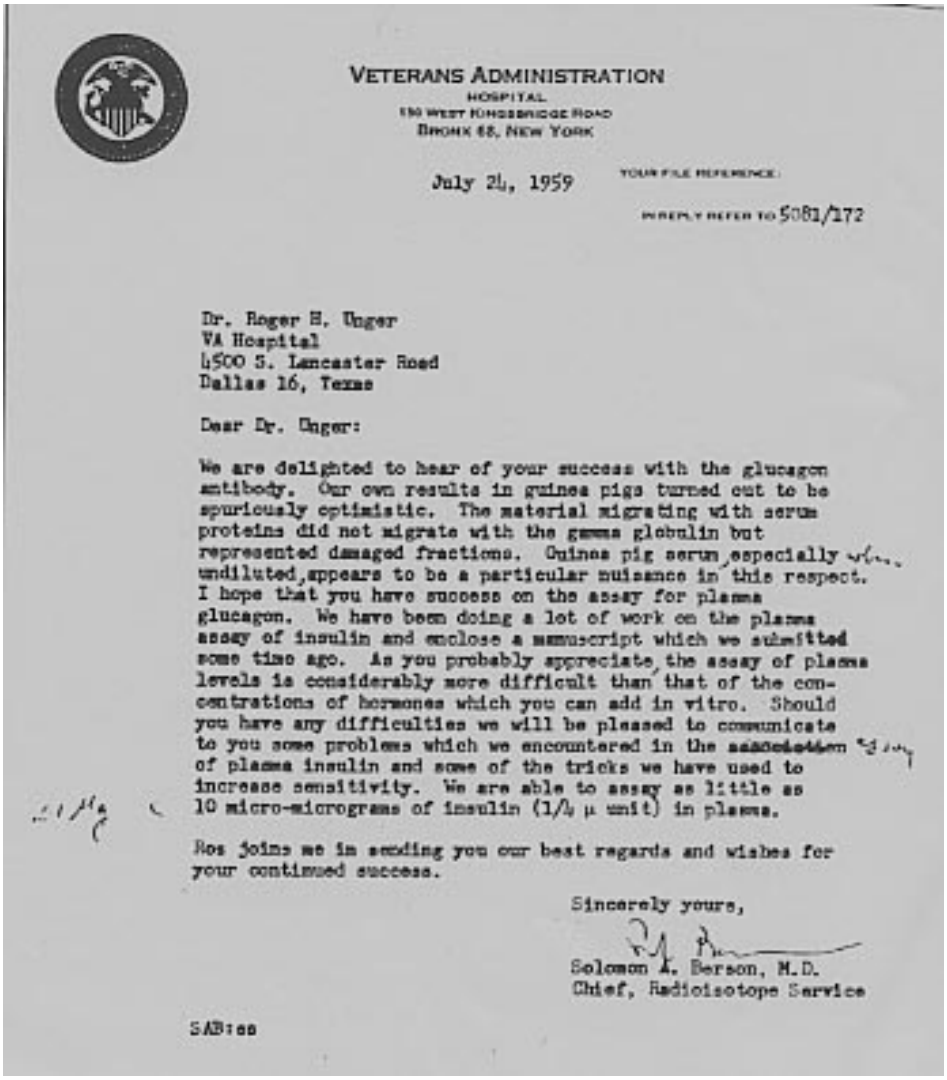
> "I was interested in the pathophysiology of carbohydrate metabolism—diabetes. The big need in those days was to be able to measure peptide hormones in the plasma.... We tried to

reproduce (a red cell) assay for insulin and glucagons. I had the idea that glucagon was a very important player in carbohydrate metabolism along with insulin, and we wanted an assay for both. We used this red cell immunoassay, and it was very, very insensitive. It only measured milliunits of insulin, so it was useless. But the idea of competitive inhibition using antibodies, I thought, was a good one. So in 1952 Berson published his first paper on detecting insulin antibodies in the plasma of insulin-dependent diabetics using labeled insulin, ^{131}I labeled insulin. So my idea was – well, instead of using red cells, why not use ^{131}I?"

Unger did not know Dr. Berson, but telephoned him anyway to discuss his idea. Unger related that he was invited to the Bronx VA Hospital, where Berson and Rosalyn Yalow were doing research that would later lead to a Nobel Prize:

"I went up to the Bronx VA and ... she (Dr. Yalow) came in with a pile of notebooks and she showed me the data. She had a beautiful curve for an insulin assay. They had already had this idea and finished it.

"I said, 'Why did you not publish anything?' He (Berson) said 'We're having an awful lot of trouble getting this article published.' He showed me the preprint. So I said, 'Well, look, Dr. Berson, since you've already worked out the insulin assay, why don't I just go on ahead and work on the glucagon assay?' He said 'You're welcome to try that. We've been trying it for two or three years, and I'll tell you right now, you can't get glucagon antibody since it's not allergenic.' I said, 'We've already immunized a bunch of rabbits. I mean, we've already challenged a bunch of rabbits with glucagon for this RBC assay, but it is too insensitive. Why don't you teach me how to iodinate glucagon, and I'll go back and use your technique to see if



VETERANS ADMINISTRATION
HOSPITAL
130 WEST KINGSBRIDGE ROAD
BRONX 68, NEW YORK

July 24, 1959

YOUR FILE REFERENCE:

IN REPLY REFER TO 5081/172

Dr. Roger H. Unger
VA Hospital
4500 S. Lancaster Road
Dallas 16, Texas

Dear Dr. Unger:

We are delighted to hear of your success with the glucagon antibody. Our own results in guinea pigs turned out to be spuriously optimistic. The material migrating with serum proteins did not migrate with the gamma globulin but represented damaged fractions. Guinea pig serum, especially undiluted, appears to be a particular nuisance in this respect. I hope that you have success on the assay for plasma glucagon. We have been doing a lot of work on the plasma assay of insulin and enclose a manuscript which we submitted some time ago. As you probably appreciate, the assay of plasma levels is considerably more difficult than that of the concentrations of hormones which you can add in vitro. Should you have any difficulties we will be pleased to communicate to you some problems which we encountered in the assay of plasma insulin and some of the tricks we have used to increase sensitivity. We are able to assay as little as 10 micro-micrograms of insulin (1/4 μ unit) in plasma.

Ros joins me in sending you our best regards and wishes for your continued success.

Sincerely yours,

Solomon A. Berson, M.D.
Chief, Radioisotope Service

SAB:ss

Figure 7.7. Collegial letter from Solomon Berson to Roger Unger

there are any antibodies?' He taught me how to iodinate, and I went back to Dallas and did, in fact, find glucagon antibodies.

"So we published a paper in 1959,[40] which really, in terms of date, was the first RIA paper ever published. We knew that they (Berson and Yalow) were having publication problems with a prior article, so I wrote them to ask permission—could we go on ahead and publish this paper? There was no published record of their work that I could cite to give them the credit that they deserved. Their paper didn't come out until 1960. They did have a paragraph in *Advances in Nuclear Medicine* in 1958, I think, that I was able to cite to give them the proper credit, and they told me to go ahead. I offered to hold the paper back until after theirs was published, but they said 'No, go ahead.'"[31]

Oakland–Pathology

At the Oakland (Calif.) VA Hospital, set in an old hotel, Bruno Gerstl, M.D. and his colleagues were systematically collecting increasingly sophisticated clinical data. Tuberculosis was still a clinical problem of great interest. Gerstl's group found that circulating antibodies of the common type were absent in pulmonary tuberculosis,[41] but that antibodies were detectable by a new method.[42] They studied the electrophoretic patterns of the lipoproteins in spinal fluid and the effects of diet on the pattern of unsaturated fats.[43, 44] They correlated X-ray findings with pathology, especially in pulmonary diseases.[45-47]

Los Angeles–Gastroenterology

At the Wadsworth VA Hospital in Los Angeles, James Halsted, M.D., Chief of Gastroenterology, was collaborating on studies of the effects of stress on the upper gastrointestinal tract.[48, 49] His most important contributions during this period were on the absorption of vitamin B_{12} and its relation to megaloblastic anemia, especially in diseases of the upper gastrointestinal tract.[50-58] In 1955, Halsted moved to the Syracuse VA Hospital as Director, Professional Services (later called the Chief of Staff), and Morton Grossman came to Wadsworth to head gastroenterology. Grossman was already beginning his work on gastrointestinal hormones[59, 60] but his work during the 1950s reflected broad interests. He studied gastro-esophageal reflux,[61] experimental pancreatitis,[62] Laennec's cirrhosis[63, 64] and a new nuclear medicine test for intestinal absorption.[65] By the end of this period, he was working on his first dog model for the experimental studies of gastric secretion, for which he became famous.[66]

Boston–Nephrology

Among the enthusiastic staff Maurice Strauss, M.D. recruited to the Boston VA Hospital was Solomon Papper, M.D. With his colleagues, Papper studied renal excretion of water and solutes in human subjects, as influenced by various conditions. They reported on sodium excretion in Addison's disease[67] and after sodium administration,[68] on ethanol effect on water diuresis,[69] and on the influence of Laennec's cirrhosis,[70-72] acute hepatitis[73] and myxedema[74] on kidney function.

Chicago Research Hospital – Physiology

In 1953, Francis Haddy, M.D. joined the brand-new Chicago Research VA Hospital, where, together with Richard Ebert, M.D., Craig Borden, M.D., Ben Heller, Ph.D., and John A.D. Cooper, M.D., Chief of Nuclear Medicine (Chapter 6), he set up the clinical and research facilities. He returned to the Research Hospital in 1957 as one of the early Clinical Investigators. Morris Lipton, M.D., Ph.D., was then the associate director for research in Chicago, a position he held until 1957, when Haddy assumed it until leaving in 1959.[75] Haddy and Lipton collaborated on studies of serotonin and its interaction with the catecholamines.[76, 77] Haddy expanded the work he had done in the Army[78] on factors influencing blood flow to a series of animal studies on regulation of blood flow.[79-85]

Thomas Starzl, M.D., was at the Research Hospital at that time and was already transplanting livers in dogs, though without success.[86] Starzl later achieved the first successful human liver transplant while at the Denver VA Hospital.

Des Moines–Surgery

At Des Moines, Iowa, L.T. Palumbo, M.D., Chief of Surgery, published extensive follow-up evaluations of large series of patients treated by established and innovative surgical procedures: on the physiological changes caused by vagotomy, with or without gastrectomy,[87-89] and on results of various types of hernia repair (1650 cases).[90, 91] He worked extensively on methods to avoid Horner's syndrome when doing upper sympathectomy,[92-94] and studied the physiology of the sympathetic pathways to the eye.[95, 96]

Birmingham–Cardiology

At the Birmingham (Ala.) VA Hospital, E.E. Eddleman, M.D. was studying, in humans and dogs, the motions made by the heart as measured externally by kinetocardiography or ballistocardiography.[97-104]

San Fernando–Mycology

At the San Fernando (Calif.) VA Hospital, a tuberculosis hospital later destroyed in an earthquake, Milton Huppert, Ph.D. was beginning his research in mycology. Huppert later became known as an authority on coccidioidomycosis. From 1955 through 1959, he published on this condition, [111] as well as on candida albicans infections,[105, 106] atypical mycobacteria[107, 108] and fungal infections of the skin.[109, 110]

Chicago Westside–Hematology

Paul Heller, M.D., later acclaimed for his clinical and basic research on the hemoglobinopathies and made a Senior Medical Investigator in 1969, met Hyman Zimmerman, M.D. when both were in Washington, D.C. Zimmerman (Chapter 3) recruited Heller to the Omaha (Neb.) VA Hospital in 1951 and then to the Chicago Westside VA Hospital in early 1954. After joining VA, Heller collaborated with Zimmerman in an eclectic research program: clinical studies of hepatic dysfunction,[112-116] studies of nucleophagocytosis,[117, 118] serum enzyme patterns in disease[119-121] and Vitamin B12 distribution in the rat.[122] Encouraged by Zimmerman, Heller began to study and publish on the hemoglobins.[123-126] Heller's later work on abnormal hemoglobin diseases, especially sickle cell anemia and sickle cell trait, later won him the Middleton Award (Chapter 18).

Buffalo–Cardiac Pacemaker

When Andrew Gage, M.D., started work as a surgeon at the Buffalo (N.Y.) VA Hospital around 1953, fresh out of his residency, William Chardack, M.D. was the hospital's Assistant Chief of Surgery. Gage and Chardack organized a one-room animal research facility in an old laundry area. In that room, they housed dogs, kept apparatus, and set up the animal studies operating room. After

about a year, they added another room and were able to house the dogs separately. One research employee took care of the animals, assisted at surgery and did a wide variety of other tasks.

Around 1954, Gage and Chardack began to work on coronary revascularization and blood flow. They studied mortality in dogs after coronary ligation. Gage worked out a system of putting thrombogenic wires into coronary arteries.[127] After the dogs developed ischemia, they were used to study the Beck and Vineberg operations, early procedures directed to coronary artery stenosis.[128]

In 1958, Chardack and Gage started the work that led to developing an artificial pacemaker. In their coronary studies, they assembled a lot of physiology equipment but were having problems with it. They hired Wilson Greatbatch, an electrical engineer who was then a private consultant, to assist them. He asked if there might be some use for a device to stimulate the heart and they said that they would be interested in seeing such a device. Greatbatch built one and brought it back; the researchers attached it to a dog's heart and it worked for 20 seconds before failing. This was the beginning of the work that led to the clinically applicable pacemaker. The concept of pacing the heart had been tried in England and reported not to be feasible, but Gage and Chardack had not seen the paper.[129] During the following year, they studied many dogs with increasing success[130] in their tiny laboratory supported by VA general medical research funds.

In 1959, they had a visit from John Kennedy, M.D. the Director of Surgery, and Lyndon Lee, M.D. the Chief of Surgery Research, in Central Office. The investigators were able to show the visitors a dog with complete heart block that was kept alive with the pacemaker. Very impressed, Kennedy and Lee arranged for additional funds to enlarge the facility.

This successful implantable pacemaker[131] was first described at the December 1959 VA annual research meeting held in Cincinnati.[129]

First NAS-NRC survey of VA research

In the late 1950s, at the request of the VA Administrator, the National Academy of Sciences-National Research Council (NAS-NRC) began the first of its three surveys of VA's research program. Why VA requested these surveys is uncertain, but it seems likely that its leaders wanted to be reassured of the value of the program and also to acquire an objective source to quote in support of it.

While the NAS-NRC report was not published until June 1960, the actual review occurred in 1958 and 1959. In the process, hospitals were visited, deans and research investigators interviewed, and many documents reviewed. The report concluded that "There is no question but that the Veterans Administration has good reason to be proud of the quality of its research now."[132]

This report recommended that central coordination by Central Office Research Service and decentralized administration be continued for VA's medical research program. "It has proved both effective and efficient to give autonomy in the use of research funds and responsibility for the quality and pertinency of research to the local Veterans Administration stations."[133] This report also encouraged expansion of the Research Service staff in Central Office by the "addition of three or four persons who are highly skilled in research methods and research administration."[134]

The report compared the 1958 VA research publications in more prestigious journals with those from the NIH's intramural program. In general, more NIH publications appeared in basic journals such as the *American Journal of Physiology* and the *Journal of Biological Chemistry*, while more VA publications appeared in clinically oriented journals such as the *Annals of Internal Medicine*, *JAMA*, the *New England Journal of Medicine* and the AMA Archives series. Publication in the *Journal of Clinical Investigation* was similar for the two groups: 23 NIH papers published and 27 VA papers published that year.[135]

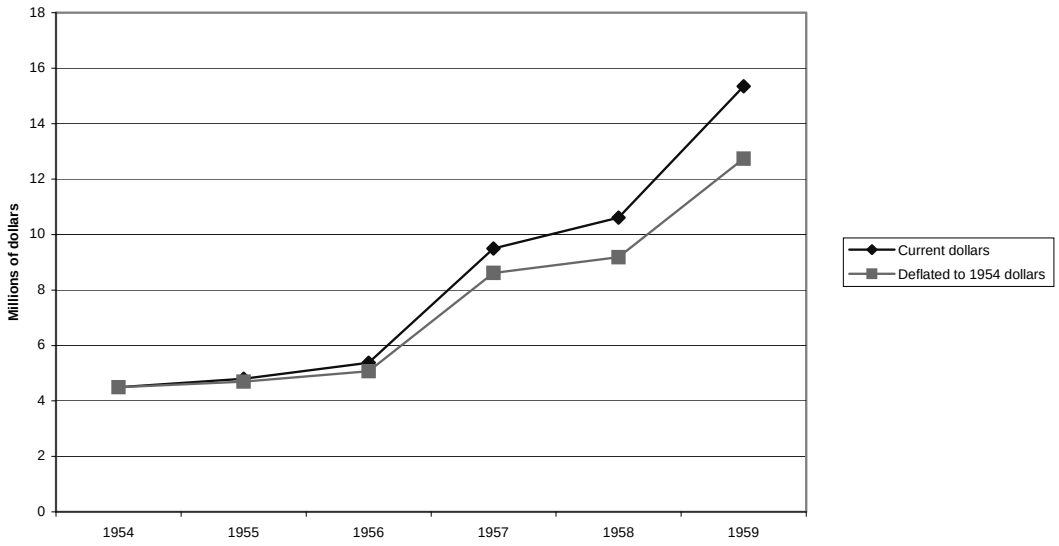
VA research at the end of the 1950s

The NAS-NRC report provided an encapsulated description of the VA medical research program in 1959. There were 6,371 approved projects, with 1,780 described as general medical research, 1,761 as studies in aging, 1,711 as investigations of mental and nervous diseases, 642 as radioisotope research, 381 as tuberculosis studies and 96 as dental research. Nine special dental research laboratories and 12 other special laboratories reported directly to Central Office. In addition, 17 tuberculosis laboratories and 34 neuropsychiatric laboratories worked closely with their counterparts in Central Office. In all, 128 VA stations operated research programs. There were 28 ongoing cooperative studies, including the study of the chemotherapy of tuberculosis, which involved 58 hospitals. This can be said to be the "golden age" of VA research.

Recalling the 1950s, Dr. Andrew Gage described the enthusiasm of VA researchers:

> "Research was motivated by academic drive and intellectual curiosity. It was easier in those days, because there was so much to be done and little to impede a motivated researcher. Devices needed to be built and physiologic studies done. One could have an idea and carry it out, and six months later a paper might be generated."[129]

Figure 7.8 Research budget, 1954-1959



References

1. *Telephone Directory, Veterans Administration Central Office*. 1954.

2. Interview with Martin Cummings, M.D., April 7, 1988 at Dr. Cumming's office in Washington, DC.

3. Lyon, G.M. "Medical research programs of the Veterans Administration." *25th meeting of the Committee on Veterans Medical Problems*. December 8, 1952. Washington, DC: National Academy of Science-National Research Council, Appendix II.

4. Interview with Martin Cummings, M.D., February 7, 1994 at Dr. Cummings' home in Florida.

5. Telephone interview with John C. Nunemaker, M.D., January 14, 1992.

6. Telephone interview with Ernest Allen, Ph.D., April 11, 1988.

7. Acting Chief Medical Director. "Appendix IV." *29th meeting of the Committee on Veterans Medical Problems*. December 8, 1952. Washington, DC: National Academy of Science-National Research Council, 633.

8. Interview with Michael DeBakey, M.D., January 28,1994 at Dr. DeBakey's office at Baylor Medical Center, Houston, TX.

9. *Medical Research in the Veterans' Administration. For the Year Beginning July 1, 1962 and Ending June 39, 1963 (Fiscal Year 1963)*. Washington, DC: U.S. Government Printing Office, 1963, 1.

10. *Medical Research in the Veterans' Administration. For the Year Beginning July 1, 1955 and Ending June 39, 1956 (Fiscal Year 1956)*. Washington, DC: U.S. Government Printing Office, 1957.

11. Interview with Stewart G. Wolf, M.D., 10/30/92 at Dr. Wolf's office in Tott's Gap, PA.

12. Interview with Marjorie T. Wilson, M.D., 4/29/88 at Dr. Wilson's office in Washington, DC.

13. Interview with Oscar Auerbach, M.D., October 30, 1992 at Dr. Auerbach's office at the East Orange, NJ VAMC.

14. Interview with Ludwig Gross, M.D., October 28, 1992 at Dr. Gross's office at the Bronx VAMC.

15. Interview with Edward Freis, M.D., April 8, 1993 at Dr. Freis's office at the Washington, DC VAMC.

16. Interview with Abraham Dury, Ph.D., February 8, 1994 at Dr. Dury's home in Florida.

17. Chamberlain, W.E., "Radiological health." *Newsletter: Research and Education in Medicine*, May, 1960. 17.

18. "Personals." *Newsletter: Research and Education in Medicine*, September, 1960. 28.

19. *Medical Research in the Veterans' Administration. For the Year Beginning July 1, 1959 and Ending June 30, 1960 (Fiscal Year 1960).* Washington, DC: Government Printing Office, 1960, 37-81.

20. *Medical Research in the Veterans' Administration, FY 1960.* 1960, 11.

21. *Medical Research in the Veterans' Administration, FY 1956.* 1957, 8-9.

22. *Medical Research in the Veterans' Administration, FY 1956.* 1957, 10.

23. *Medical Research in the Veterans' Administration, FY 1956.* 1957, 12.

24. *Medical Research in the Veterans' Administration. For the Year Beginning July 1, 1973 and Ending June 30, 1974 (Fiscal Year 1974).* Washington, DC: U.S. Government Printing Office, 1975, 99.

25. Felix, W.R., Myerson, R.M., Sigel, B., Perrin, E.B. and Jackson, F.C., "The effect of portacaval shunt on hypersplenism." *Surg Gynecol Obstet*, 1974. **139**: 899-904.

26. *Medical Research in the Veterans' Administration, FY 1956.* 1957, 11-12.

27. *Medical Research in the Veterans' Administration, FY 1956.* 1957, 12-13.

28. *Medical Research in the Veterans' Administration, FY 1960.* 1960, 37-82.

29. *Medical Research in the Veterans' Administration, FY 1960.* 1960, 42.

30. Eisenberg, S., Madison, L.L. and Sensenbach, W., "Cerebral hemodynamic and metabolic studies in patients with congestive heart failure. II. Observations in confused subjects." *Circulation*, 1960. **21**: 704-709.

31. Interview with Roger H. Unger, M.D., January 27, 1994 at Dr. Unger's office at the Dallas VAMC.

32. Madison, L.L. and Unger, R.H., "Comparison of the effects of insulin and Orinase (tolbutamide) on peripheral glucose utilization in the dog." *Metabolism*, 1958. **7**: 227-239.

33. Madison, L.L. and Unger, R.H., "The physiological significance of the secretion of endogenous insulin into the portal circulation. I. Comparison of the effects of glucagon-free

insulin administered via the portal vein and via a peripheral vein on the magnitude of hypoglycemia and peripheral glucose utilization." *J Clin Invest*, 1958. **37**: 631-639.

34. Unger, R.H. and Madison, L.L., "Comparison of response to intravenously administered tolbutamide in mild diabetic and non-diabetic subjects." *J Clin Invest*, 1958. **37**: 627-630.

35. Madison, L.L., Combes, B., Strickland, W., Unger, R.H. and Adams, R., "Evidence for a direct effect of insulin on hepatic glucose output." *Metabolism*, 1959. **8**: 469-471.

36. Madison, L.L., Combes, B., Unger, R.H. and Kaplan, N., "The relationship between the mechanism of action of the sulfonylureas and the secretion of insulin into the portal circulation." *Ann NY Acad Sci*, 1959. **74**: 548-556.

37. Unger, R.H., Madison, L.L. and Carter, N.W., "Relative effectiveness of newer oral agents in the regulation of diabetic patients imperfectly controlled by tolbutamide studied within the framework of a tentative subclassification of the disease." *Ann NY Acad Sci*, 1959. **82**: 570-584.

38. Unger, R.H. and Madison, L.L., "A new diagnostic procedure for mild diabetes mellitus; Evaluation of an intravenous tolbutamide response test." *Diabetes*, 1958. **7**: 455-461.

39. Unger, R.H. and Madison, L.L., "The intravenous tolbutamide response test in diagnosis of mild diabetes." *Ann NY Acad Sci*, 1959. **74**: 667-671.

121. Heller, P., Weinstein, H., West, M. and Zimmerman, H., "Enzymes in anemia: A study of abnormalities of several enzymes of carbohydrate metabolism in the plasma and erythrocytes in patients with anemia, with preliminary observations of bone marrow enzymes." *Ann Int Med*, 1960. **53**: 898-913.

122. Heller, P., Henderson, W., Bowser, E., Levitsky, JM, and Zimmerman, H., "The distribution of Co58-labeled vitamin B12 in the rat with fatty metamorphosis and cirrhosis of the liver." *J Lab Clin Med*, 1960. **55**: 29-37.

123. Josephson, A.M., Singer, K., Singer, L., Heller, P. and Zimmerman, H., "Hemoglobin S-thalassemia and Hemoglobin C-thalassemia in siblings." *Blood*, 1957. **12**: 593-602.

124. Oliner, H. and Heller, P., "Megaloblastic erythropoiesis and acquired hemolysis in sickle-cell anemia." *N Eng J Med*, 1959. **261**: 19-22.

125. Heller, P., Weinstein, H., West, M. and Zimmerman, H., "Glycolytic, citric acid cycle, and hexosemonophosphate shunt enzymes of plasma and erythrocytes in megaloblastic anemia." *J Lab Clin Med*, 1960. **55**: 425-434.

126. Yakulis, V., Heller, P., Josephson, A. and Singer, L., "Rapid demonstration of A2 Hemoglobin by means of agar gel electrophoresis." *Am J Clin Path*, 1960. **34**.

127. Gage, A., Olsen, K. and Chardack, W., "Experimental coronary thrombosis in dog; Description of method." *Ann Surg*, 1956. **143**: 289-294.

128. Gage, A., Olsen, K. and Chardack, W., "Cardiopericardiopexy: An experimental evaluation." *Ann Surg*, 1958. **147**: 289-294.

129. Telephone interview with Andrew Gage, M.D., May 21, 1992.

40. Unger, R.H., Eisentraut, A.M., McCall, M.S., Keller, S., Lanz, H.C. and Madison, L.L., "Glucagon antibodies and their use for immunoassay for glucagon." *Proc Soc Exp Biol Med*, 1959. **102**: 621-623.

41. Gerstl, B., Kirsh, D., Davis, W., Jr. and Barbieri, M., "Absence of circulating antibodies in patients with pulmonary tuberculosis." *Science*, 1954. **120**: 853-854.

42. Gerstl, B. and others, "Detection of apparently absent circulating antibodies in tuberculous sera." *Am Rev Tuberc*, 1955. **72**: 345-355.

43. Gerstl, B., Davis, W., Jr, Smith, J., Athineos, E. and Herold, G., "Effects of dietary fat upon polyunsaturated fatty acids in patients with multiple sclerosis." *Proc Soc Exp Biol Med*, 1959. **100**: 534-538.

44. Smith, J., Gerstl, B., Davis, W., Jr. and Orth, D., "Lipoprotein patterns of spinal fluid obtained by electrophoresis." *Arch Neurol Psychiat*, 1956. **76**: 608-613.

45. Epstein, E., Gerstl, B., Bark, M. and Belber, J., "Silica pregranuloma." *Arch Dermat*, 1955. **71**: 645-647.

46. Jacobs, L. and Gerstl, B., "Effect of pulmonary tuberculosis on Roentgen shadow of heart." *Rock Mountain MJ*, 1956. **53**: 363-370.

47. Jacobs, L., Gerstl, B., Hollander, A. and Berk, M., "Intra-abdominal egg-shell calcifications due to silicosis." *Radiology*, 1956. **67**.

48. Halsted, J., "Emotional component in gastrointestinal disorders." *California Med*, 1954. **80**: 449-454.

49. Bachrach, W., Smith, J. and Halsted, J., "Spasm of the choledochal sphincter accompanying sudden stress." *Gastroenterol*, 1952. **22**: 604-606.

50. Halsted, J., Gasster, M. and Drenick, E., "Absorption of radioactive vitamin B12 after total gastrectomy; Relation to microcytic anemia and to site of origin of Castle's intrinsic factor." *N Eng J Med*, 1954. **251**: 161-168.

51. Swendseid, M., Halsted, J. and Libby, R., "Excretion of cobalt 60-labeled vitamin B12 after total gastrectomy." *Proc Soc Exper Biol and Med*, 1953. **83**: 226-228.

52. Swendseid, M., Gasster, M. and Halsted, J., "Limits of absorption of orally administered vitamin B12: Effect of intrinsic factor sources." *Proc Soc Exper Biol and Med*, 1954. **86**: 834-836.

53. Halsted, J., "Megaloblastic anemia associated with surgically produced gastrointestinal abnormalities." *California Med*, 1955. **83**: 212-217.

54. Halsted, J., Swenseid, M., Gasster, M. and Lewis, P., "Absorption of radioactive vitamin B12 in patients with disease of small intestine: Relation to macrocytic anemia." *Trans Amer Clin Climat Assn*, 1955. **66**: 18-36.

55. Halsted, J., Swenseid, M., Lewis, P. and Gasster, M., "Mechanisms involved in development of vitamin B12 deficiency." *Gastroenterology*, 1956. **30**: 21-36.

56. Halsted, J. and others, "Evaluation of fecal recovery method for determining intestinal absorption of vitamin B12." *J Lab Clin Med*, 1956. **48**: 92-101.

57. Citrin, Y., DeRosa, C. and Halsted, J., "Sites of absorption of vitamin B12." *J Lab Clin Med*, 1957. **50**: 667-672.

58. Halsted, J., Carroll, J. and Rubert, S., "Serum and tissue concentration of vitamin B12 in certain pathologic states." *N Eng J Med*, 1959. **260**: 575-580.

59. Grossman, M., "The physiology of secretin." *Vitamins and Hormones, NY*, 1958. **16**: 179-203.

60. Grossman, M., "Some properties of trypsin inhibitor of pancreatic juice." *Proc Soc Exp Biol Med*, 1958. **99**: 304-306.

61. Tuttle, S. and Grossman, M., "Detection of gastro-esophageal reflux by simultaneous measurement of intraluminal pressure and pH." *Proc Soc Exp Biol Med*, 1958. **98**: 225-227.

62. Grossman, M., "Experimental pancreatitis: Recent contributions." *JAMA*, 1959. **169**: 1567-1570.

63. Grossman, M., "Hepatic coma." *Gastroenterology*, 1958. **34**: 667-674.

64. Tuttle, S., Figueroa, W. and Grossman, M., "Development of hemochromotosis in a patient with Laennec's cirrhosis." *Am J Med*, 1959. **26**: 655-658.

65. Grossman, M. and Jordan, P., Jr, "The radio-iodinated triolein test for steatorrhea." *Gastroenterology*, 1958. **34**: 892-900.

66. Grossman, M., "Stimulation of secretion of acid by distention of denervated fundic pouches in dogs." *Gastroenterology*, 1961. **41**: 385-390.

67. Rosenbaum, J., Papper, S. and Ashley, M., "Variations in renal excretion of sodium independent of change in adrenocortical hormone dosage in patients with Addison's disease." *J Clin Endocr*, 1955. **15**: 1459-1474.

68. Papper, S., Saxon, L., Rosenbaum, J. and Cohen, H., "Effects of isotonic and hypotonic salt solutions on renal excretion of sodium." *J Lab Clin Med*, 1956. **47**: 776-782.

69. Rosenbaum, J., Papper, S., Cohen, H. and McLean, R., "The influence of ethanol upon maintained water diuresis in man." *J Clin Invest*, 1957. **36**: 1202-1207.

70. Papper, S., "The role of the kidney in Laennec's cirrhosis of the liver." *Medicine, Balt*, 1958. **37**: 299-316.

71. Papper, S. and Saxon, L., "The diuretic response to administered water in patients with liver disease. II. Laennec's cirrhosis of the liver." *Arch Int Med*, 1959. **103**: 750-757.

72. Papper, S., Belsky, J. and Bleifer, K., "Renal failure in Laennec's cirrhosis of the liver. I. Description of clinical and laboratory features." *Ann Intern Med*, 1959. **51**: 759-773.

73. Papper, S., Seifer, H. and Saxon, L., "The diuretic response to administered water in patients with liver disease. I. Acute infectious hepatitis." *Arch Int Med*, 1959. **103**: 746-749.

74. Bleifer, K., Belsky, J., Saxon, L. and Papper, S., "The diuretic response to administered water in patients with primary myxedema." *J Clin Endocr*, 1960. **20**.

75. Telephone interview with Francis Haddy, M.D., Ph.D., April 6, 1988.

76. Gordon, P., Haddy, F. and Lipton, M., "Serotonin antagonism of noradrenalin in vivo." *Science*, 1958. **128**: 531-532.

77. Haddy, F., "Serotonin and the vascular system." *Angiology*, 1960. **11**: 21-24.

78. Emanuel, D., Scott, J. and Haddy, F., "Effect of potassium on small and large blood vessels of the dog forelimb." *Amer J Physiol*, 1959. **197**: 637-642.

79. Haddy, F., "Vasomotion in large and small blood vessels." *Illinois Med J*, 1958. **114**: 107-111.

80. Haddy, F., "Effect of histamine on small and large vessel pressures in the dog foreleg." *Amer J Physiol*, 1960. **198**: 161-168.

81. Haddy, F., "Local effects of sodium, calcium and magnesium upon small and large blood vessels of the dog forelimb." *Circ Res*, 1960. **8**: 57-70.

82. Haddy, F., "Peripheral vascular resistance." *Amer Heart J*, 1960. **60**: 1-5.

83. Haddy, F., "Effect of levarterenol upon venous pressure in the rabbit ear." *Angiology*, 1961. **12**: 486-490.

84. Haddy, F., "Autoregulation of blood flow." *Amer Heart J*, 1961. **62**: 565-566.

85. Haddy, F., Molnar, J. and Campbell, R., "Effects of denervation and vasoactive agents on vascular pressures and weight of dog forelimb." *Amer J Physiol*, 1961. **201**: 631-638.

86. Starzl, T.E., *The Puzzle People: Memoirs of a Transplant Surgeon*. Pittsburgh and London: University of Pittsburgh Press, 1992, 62.

87. Palumbo, L., "Physiological changes of upper gastrointestinal tract following combined partial gastrectomy and vagus resection." *Mississippi Valley Med J*, 1954. **76**: 56-60.

88. Palumbo, L., Mazur, T. and Doyle, B., "Combined vagus resection and partial gastrectomy for duodenal and marginal ulcer." *Arch Surg*, 1954. **69**: 762-768.

89. Palumbo, L., Mazur, T. and Doyle, B., "Partial gastectomy with or without vagus resection for duodenal or marginal ulcer." *Surgery*, 1954. **36**: 1043-1050.

90. Palumbo, L. and Mighell, S., "Primary indirect inguinal hernioplasty." *Am J Surg*, 1954. **88**: 293-297.

91. Palumbo, L. and Mighell, S., "Primary direct inguinal hernioplasty; Study of 275 Cases." *Surgery*, 1954. **36**: 278-282.

92. Palumbo, L., "Upper dorsal sypmpathectomy without Horner's syndrome." *Arch Surg*, 1955. **71**: 743-751.

93. Palumbo, L., "Anterior transthoracic approach for upper thoracic sympathectomy." *Arch Surg*, 1956. **72**.

94. Palumbo, L., "New surgical approach for upper thoracic sympathectomy; a method to avoid Horner's syndrome." *Arch Surg*, 1958. **76**: 807-810.

95. Palumbo, L., "A new concept of the sympathetic pathways to the eye; a new technique to avoid a Horner's syndrome." *Surgery*, 1957. **42**: 740-748.

96. Palumbo, L. and Shapiro, S., "Physiological studies before and after upper dorsal sympathectomy." *Ann Surg*, 1958. **147**: 261-263.

97. Eddleman, E.E., Jr. and Reeves, T.J., "Kinetocardiography." *Meth Med Res*, 1958. **7**: 107-118.

98. Eddleman, E.E., Jr., "Kinetocardiographic changes as the result of mitral commissurotomy." *Am J Med*, 1958. **25**: 733-743.

99. Frederick, W.H. and Eddleman, E.E., Jr., "Genesis of the force ballistocardiogram of the dog." *J Appl Physiol*, 1958. **13**: 109-117.

100. Frederick, W.H. and Eddleman, E.E., Jr., "A simple bed suspension for ultra-low frequency ballistocardiography on dogs." *J Appl Physiol*, 1958. **12**: 347-348.

101. Suh, S.K., Cooper, W.H., Frederick, W.H. and Eddleman, E.E., Jr., "Force, work, and power ballistocardiography." *Am J Card*, 1958. **1**: 726-735.

102. Eddleman, E.E., Jr. and Thomas, H.D., "The recognition and differentiation of right ventricular pressure and flow loads." *Amer J Cardiol*, 1959. **4**: 652-661.

103. Eddleman, E.E., Jr., Hughes, M.L. and Thomas, H.D., "Estimation of pulmonary artery pressure and pulmonary vascular resistance from ultra low frequency precordial movements (kinetocardiograms)." *Amer J Cardiol*, 1959. **4**: 662-668.

104. Suh, S.K. and Eddleman, E.E., Jr., "Kinetocardiographic findings in myocardial infarction." *Circulation*, 1959. **19**: 531-542.

105. Huppert, M. and Cazin, J., Jr., "Pathogenesis of candida albicans infection following antibiotic therapy; Further studies of effect of antibiotics on in vitro growth of candida albicans." *J Bact*, 1955. **70**: 435-439.

106. Huppert, M., Cazin, J., Jr. and Smithe, H., Jr., "Pathogenesis of candida albicans infection following antibiotic therapy; Effect of antibiotics on incidence of candida albicans in intestinal tract of mice." *J Bact*, 1955. **70**: 440-447.

107. Huppert, M., Wayne, L. and Juarez, W., "Characterization of atypical mycobacteria and of nocardia species isolated from clinical specimens. II. Procedure for differentiating between acid-fast microorganisms." *Am Rev Tuberc*, 1957. **76**: 468-479.

108. Wayne, L., Krasnow, I. and Huppert, M., "Characterization of atypical mycobacteria and of nocardia species isolated from clinical specimens. I. Characterization of atypical mycobacteria by means of the microcolonial test." *Am Rev Tuberc*, 1957. **76**: 451-467.

109. Huppert, M. and Keeney, E., "Immunization against superficial fungous infection. II. Studies on human volunteer subjects." *J Invest Derm*, 1959. **32**: 15-19.

110. Keeney, E. and Huppert, M., "Immunization against superficial fungous infection. I. Studies on experimental animals." *J Invest Derm*, 1959. **32**: 7-13.

111. Huppert, M. and Walker, L., "The selective and differential effects of cyclohexamide on many strains of coccidioides immetis." *Am J Clin Path*, 1958. **29**: 291-295.

112. Heller, P., Korn, R. and Zimmerman, H., "Amebic hepatitis presenting as fever of unknown origin." *N Eng J Med*, 1953. **249**: 596-600.

113. Loomis, G., Heller, P., Hall, W. and Zimmerman, H., "Pattern of hepatic dysfunction in malaria." *Am J Med Sci*, 1954. **227**: 408-416.

114. Heller, P., Zimmerman, H., Rozengvaig, S. and Singer, K., "L.E. - cell phenomenon in chronic hepatic disease." *N Eng J Med*, 1956. **254**: 1160-1165.

115. Krasnow, S., Walsh, J., Zimmerman, H. and Heller, P., "Megaloblastic anemia in alcoholic cirrhosis." *Arch Int Med*, 1957. **100**: 870-880.

116. Korn, R., Kellow, W., Heller, P., Chomet, B. and Zimmerman, H., "Hepatic involvement in extrapulmonary tuberculosis: Histological and functional characteristics." *Am J Med*, 1959. **27**: 60-71.

117. Zimmerman, H.J., Walsh, J. and Heller, P., "Production of nucleophagocytosis by rabbit antileukocytic serum." *Blood*, 1953. **8**: 651-654.

118. Heller, P. and Zimmerman, H., "Nucleophagocytosis; Studies of 336 patients." *Arch Int Med*, 1956. **97**: 208-224.

119. West, M., Heller, P. and Zimmerman, H., "Serum enzymes in disease. III. Lactic dehydrogenase and glutamic oxalacetic transaminase in patients with leukemia and lymphoma." *Am J Med Sci*, 1958. **235**: 689-701.

120. Zimmerman, H., West, M. and Heller, P., "Serum enzymes in disease. II. Lactic dehydrogenase and glutamic oxalacetic transaminase in anemia." *Arch Int Med*, 1958. **102**: 115-123.

130. Chardack, W.M., "Recollections - 1958-1961." *PACE*, 1981. **4**: 592-596.

131. Chardack, W., Gage, A. and Greatbatch, W., "A transistorized, self-contained, implantable pacemaker for the long-term correction of complete heart block." *Surgery*, 1960. **48**: 643-654.

132. Committee on the Survey of Medical Research in the Veterans Administration *Medical Research in the Veterans Administration: Final Report.* National Academy of Science - National Research Council, 1960. 45.

133. NAS Committee on VA Research *Final Report.* 1960. 2.

134. NAS Committee on VA Research *Final Report.* 1960. 3.

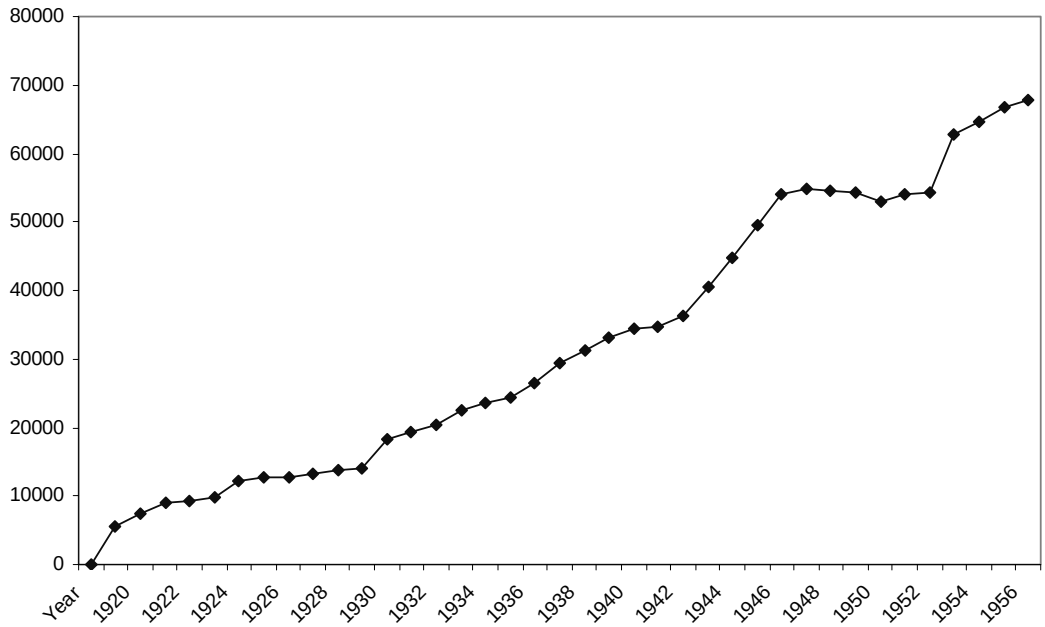
135. NAS Committee on VA Research *Final Report.* 1960. 102-103.

Chapter 8. VA Psychopharmacology Trials Lead a Revolution in Psychiatric Practice

Post-war VA Central Office direction of psychiatric research

New enthusiasm for research in mental health emerged after World War II, with the establishment of the Department of Medicine and Surgery and the affiliations with medical schools that began in 1946 (Chapter 3). Even as hospitals retooled to care for increasing numbers of patients with psychiatric disorders (Figure 8.1), the Central Office leadership recognized a need to create research programs focused on mental health. Research Chiefs for both psychiatry and psychology were recruited. While they increasingly interacted with leaders of the fledgling Research Service, these chiefs were quite independent of Research Service and reported to their superiors in Neuropsychiatry Service (Chapter 3). The Chiefs were charged with designing and supervising research of importance to VA's neuropsychiatric patients.

Figure 8.1 Neuropsychiatric patients in VA hospitals



Background—the psychoactive drugs

Since the 1950s, the explosive growth of effective psychopharmacological agents has revolutionized care of the seriously mentally ill. Prior to 1950, no genuinely effective psychoactive drugs were available to psychiatrists. There were sedatives and hypnotics, such as barbiturates, hyoscine, and chloral hydrate for insomniac, violent, anxious or agitated patients. However, few physicians seriously believed that these drug interventions actually treated psychiatric illness. At best, the medications relieved symptoms; at worst, they restrained patients chemically rather than physically and sometimes proved to be harmful.[1]

In 1950, this situation began to change when the French pharmaceutical firm Rhône-Poulenc synthesized chlorpromazine (Thorazine). Though originally synthesized for its antihistaminic properties, a number of physicians noticed its ability to create a "euphoric quietude" without undue sedation. Beginning in 1952, an increasing number of publications extolled chlorpromazine's virtue for treating psychiatric patients and, by the mid- to late 1950s, it had become one of the most successful pharmaceutical agents synthesized.[2] Almost simultaneously, Western physicians "discovered" derivatives of the alkaloid *Rauwolfia serpentina*, which had been used for centuries in India. Its Western use as an anti-hypertensive agent as well as a psychotropic agent briefly rivaled the perceived tranquilizing ability of chlorpromazine.[3] Also serendipitously, physicians in the early 1950s found that monoamine oxidase inhibitors could relieve depression and, in the mid- to late 1950s, that depressed patients responded favorably to the tricyclic imipramine. Thus, by the end of the 1950s, pharmaceutical companies had synthesized all major classes of what became a contemporary psychopharmacopoeia—including minor tranquilizers, such as the benzodiazepines.[4]

New psychopharmacologic agents intensified psychiatrists' growing recognition that they needed better methods for evaluating therapeutic interventions. In the 1930s, a surge of "revolutionary" therapies promised highly optimistic rates of cure, according to the best contemporary scientific evidence. For example, physicians of the 1930s and 1940s saw prefrontal lobotomy as the most scientifically validated therapy in their armamentarium, a belief reinforced when its inventor won the Nobel Prize in 1947.[5] Lobotomy's luster soon faded with the introduction of chlorpromazine and the realization that lobotomy may not have been as effective as originally believed.[6-8] Insulin shock therapy, too, faced a similar fate as investigators increasingly questioned its efficacy (Chapter 2). In short, psychiatrists, like their counterparts in general medicine, became aware of the pitfalls of simple clinical, albeit "expert," observation in deciding whether an intervention worked or not. Bias, the lack of valid comparison groups, and difficulties in objectively measuring outcomes made 1950s researchers increasingly wary of 1930s and 1940s studies of treatment outcome.[9]

With growing disillusionment about older remedies and the proliferation of new psychotropic drugs, psychiatric researchers began employing methods we now commonly associate with randomized controlled clinical trials. However, clinical trials posed particularly thorny problems because psychiatric disorders proved difficult to define clearly and outcomes were often vague and difficult to quantify. Further, many psychiatrists believed in the unique nature of the doctor-patient relationship that clinical trials appeared to efface.[10] However, VA investigators led the way in surmounting these difficulties, developing methodologies and carefully nurturing relevant studies. By the mid-1970s, large, multi-center clinical trials had become generally accepted as the unquestionable means for establishing preferred treatment of mental illness. VA researchers played a critical role in this process.

Early VA research in psychiatry

Before World War II, psychiatry research in VA, as elsewhere, was limited in scope, despite the large and growing number of patients hospitalized for neuropsychiatric illnesses. A centrally funded laboratory at the Northport (N.Y.) VA Hospital carried out work on shock therapies as well as more basic studies (Chapter 2). In the1920s and early 1930s, articles in the VA *Medical Bulletin* reflected a thoughtful approach to psychiatric problems in some neuropsychiatric hospitals. But by

the late 1930s and early 1940s there is little evidence of searches for better treatments. During World War II, a time when psychiatry generally received increasing recognition, VA psychiatry suffered from a severe shortage of psychiatrists. Many psychiatrists and other doctors joined the military services. VA research in general and psychiatric research in particular, seems almost to have ceased.

The lobotomy study

In this setting, in 1949, Richard L. Jenkins, M.D., Chief, Research in Psychiatry, and J. Quinter Holsopple, Ph.D., Chief, Research in Psychology, reviewed the records of some 1,500 VA patients who had received lobotomy operations. They concluded that, while there was "clear consensus that benefits did accrue to operated patients…such benefits were not reflected with equal clarity in discharge rates or in social and economic independence."[11] Evaluation of lobotomized patients as seen in the literature still heavily depended on case reports and small, uncontrolled series. Jenkins and Holsopple sought a more objective evaluation and designed a prospective study of the effects of prefrontal lobotomy. They recruited Maurice Lorr, Ph.D., VA Chief of Research in Outpatient Psychiatry, to design objective psychological scales to evaluate clinical status of study patients before surgery and at intervals after the operation.

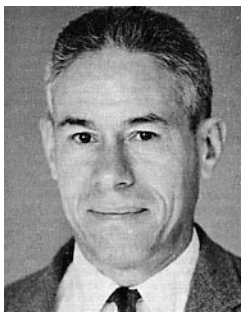


Figure 8.2. Maurice Lorr, Ph.D.

In setting up this study and later in starting the psychopharmacology studies, they drew heavily on the experience of leaders of the early VA tuberculosis studies (Chapter 5). The research problems were similar: Most of the people carrying out the day-to-day aspects of the studies at the hospitals had little or no prior research experience. Psychiatric hospitals, like tuberculosis hospitals, tended to be isolated and generally were not affiliated with medical schools. The study outcome measures depended heavily on clinical observations; it was difficult to make them objective. And it was also difficult to conceal from evaluators which treatment a patient had received.

Despite these obstacles, Jenkins, Holsopple and Lorr designed a study that, in the context of its time and subject, has been described as "model science."[12] Six VA hospitals participated and, between 1950 and 1953, 373 patients were studied: 188 who received lobotomies and 185 controls. All patients were reviewed and judged appropriate for lobotomy before they were assigned to the group having the operation or the control group that did not undergo lobotomy. However, modern randomization methods were not followed strictly: Many controls were those whose families refused the operation. "Controls were matched as closely as possible with the patients selected for lobotomy."[13] The operating surgeon decided on the type of surgery, so that the data analysis

included four different types of operations, though 140 of the 188 operated patients received the "standard" lobotomy procedure.

Patients were studied prior to the operation, with the controls studied shortly after randomization, and at three months and one, two, three, four and five years after surgery or entry into the study. The key evaluation instrument, the Multidimensional Scale for Rating Psychiatric Patients (MSRPP), was developed for the study by Lorr and his colleagues. Other clinical and psychometric observations were also recorded.

During the years of the study follow-up, chlorpromazine and other effective drugs came into increasing use in the treatment of schizophrenia. As time went on, more patients in the study were treated with these agents. At the time of the three-year follow up, one-fifth of the patients evaluated were on the drugs; by five years, two-thirds. Drug treatment made interpretation of lobotomy effects difficult.

On average, the lobotomy study showed some improvement in lobotomized patients compared to controls, as reflected in significantly higher discharge rates at three and four years. By five years, however, drug therapy had diluted the picture and the differences between the groups had diminished.

Though its conclusions were unimpressive, this study provided a template for psychopharmacology studies that followed. It provided tools to evaluate results of psychiatric treatment. As Jenkins told the Committee on Veterans Medical Problems in December 1952, before the neuroleptic drugs were in widespread use:

> "The VA lobotomy research project, under Dr. Holsopple and myself of Central Office, is being carried on in VA hospitals at Roanoke, Bedford, Northampton, Fort Custer, North Little Rock and American Lake, with very little special assistance. We regard it as significant, not only because it is yielding fairly clean-cut results upon the effects of lobotomy, but even more because we believe we have devised methods for determining and recording the effects of a treatment measure upon psychiatric patients more satisfactorily than it has been done before. These methods we believe to have an importance, which extends far beyond lobotomy. Central among them is the Multidimensional Patient Rating Scale, devised by Dr. Maurice Lorr of the Psychology Section, Central Office, which we believe to be a much more reliable, comprehensive and useful device for recording comparable data about different patients, and about the same patient at different times, than any other with which we are acquainted."[11]

The Central Neuropsychiatric Research Laboratory

In 1955, Holsopple and the lobotomy study staff moved from Central Office to the VA hospital at Perry Point on the Chesapeake Bay in northern Maryland. The hospital's administration turned over a building for research purposes, and the Central Neuropsychiatric Research Laboratory (CNPRL) was started there, with Holsopple serving as its first chief. This move was a turning point in VA's clinical psychiatric research program. The laboratory, though supported by Central Office, now became a distinct entity. It had more space than before and the staff now had access to patients and collaborations with physicians and psychologists at the hospital. Perry Point at that time was a

neuropsychiatric hospital with a moderately active research program. Twenty-eight research studies involving 48 investigators were ongoing there at the time of VA's first report to Congress for FY 1956.

The CNPRL was the focus for VA cooperative studies in psychiatry over the next two decades. Its staff, with their advisors, chose and designed studies, developed methodologies, and coordinated data collection and analysis. Together with Central Office colleagues, CNPRL managed the annual VA research conferences on chemotherapy in psychiatry. They came to know the clinicians at the participating hospitals and worked closely with them. The annual conferences and other contacts were important to morale and to assuring that these difficult studies were successful.

First VA trial of chemotherapy in psychotic disease

Even before completion of the lobotomy study, Holsopple and Jenkins began to plan a similar study of the new psychotropic drugs appearing on the scene. During the 1950s, the use of drugs in major psychiatric illness increased rapidly. Like lobotomy, these new interventions achieved widespread use: A survey in January 1957 showed that 50 percent of the 57,000 patients with psychiatric diseases hospitalized in VA hospitals were receiving tranquilizing drugs. Of those on tranquillizers, 61 percent received chlorpromazine and 21 percent reserpine or other Rauwolfia extracts.[14]

On the other hand, in the early 1950s there was no clear evidence for the efficacy of these drugs. Dosage and administration schedules were empirical. It wasn't known for sure if they did more than simply sedate patients. One of the early studies of these drugs, rare in that it was a randomized blinded study, was conducted by an internist who later played an important role in the VA psychopharmacology cooperative studies. In 1953, Leo Hollister, M.D., Chief of Medicine at the Palo Alto VA Hospital, then a psychiatric facility, noted that when he gave reserpine to treat hypertension in patients who were also schizophrenic, the patients' schizophrenic symptoms seemed to improve. He learned that others were using reserpine to treat psychotic symptoms, and he decided to confirm his impressions with a double-blind study. He persuaded some of his psychiatrist colleagues to refer acutely ill schizophrenic patients to him. They were treated with

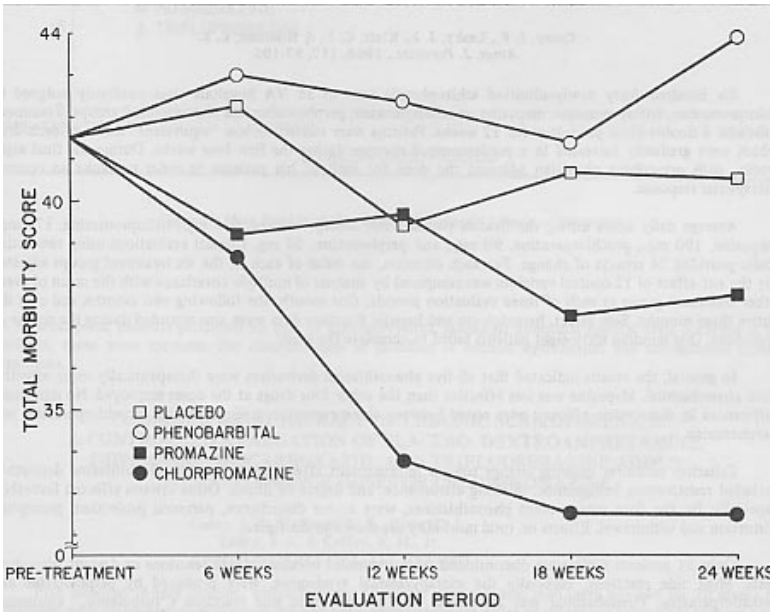
Figure 8.3. Leo Hollister, M.D.

reserpine or placebo, following a random assignment design blinded to both the patient and referring physician, and sent back to the referring psychiatrist for evaluation after three weeks of treatment on Hollister's ward. The reserpine-treated patients had improved dramatically. [15,16] When Jenkins and Holsopple assembled a group to plan the new cooperative studies, Hollister was invited to participate.

The group convened by Jenkins and Holsopple reflected a variety of interests and areas of expertise in behavioral science research. In addition to Hollister, Jenkins, Holsopple and Lorr, the original group included Gilbert Beebe , Ph.D., (statistician) and Jonathan Cole, M.D., (psychiatrist) from the National Academy of Sciences, Charles Chapple (internist) from Central Office Research Service, S.T. Ginsberg. M.D. and Clyde Lindley, M.A. from Central Office Psychiatry Service, Harry Goldsmith, M.D. from the Baltimore Regional Office and Ivan F. Bennett, M.D., Eugene Caffey, M.D., Ian Funk, M.D. and Amedeo Marrazzi, M.D., psychiatrists from VA hospitals at Coatesville (Pa.), Perry Point (Md.), Albany (N.Y.) and Pittsburgh. Their first task was to help design a study aimed at determining the efficacy of the new drugs. Biostatistician Gilbert Beebe of the Follow-up Agency (Chapter 4) advised them about study design.

A meeting of prospective participants was held at the Downey (Ill.) VA Hospital in April 1956, and the first study, involving 37 hospitals, was launched. This study (Figure 8.4) compared chlorpromazine, promazine, phenobarbital and placebo. It clearly showed that chlorpromazine, and less so promazine, led to improvement. Phenobarbital was no better than placebo. This study proved that the antipsychotic effects of chlorpromazine were not solely the result of sedation.[17]

Figure 8.4. Results of the first study of the efficacy of the phenothiazide drugs in schizophrenia



Such studies were difficult to perform. Sometimes patients who had been on drugs relapsed during the "washout" period before starting on study medication. Some patients refused their pills. Even though the drugs looked alike, ward staff often guessed what drug a patient was receiving, making it difficult to maintain the "blind" criterion for these studies. The planning group and CNPRL staff frankly discussed these problems and tried to find ways around them.[18]

Further role of the CNPRL

This first chemotherapy trial, which built on experience from the lobotomy study, created the template for future VA cooperative trials in psychiatry. It also institutionalized the CNPRL as the central organizing agency in future trials. Underscoring its role as a central organizing agency for cooperative trials, the CNPRL remained directly funded by VA Central Office Neuropsychiatry Service. In 1962, Edward Dunner, M.D., then Director, Research Service, attended the annual conference and enticed the group to join Research Service. After that, CNPRL was funded by Research Service as a Special Laboratory (Chapter 7) but retained close ties with Neuropsychiatry Service and its successors. The program remained much the same.

Holsopple, the founding Chief, died in 1957, not long after launch of the chlorpromazine study and before completion of the prefrontal lobotomy study. N. Norton (Ned) Springer, Ph.D., followed him as Chief for a year, and then Julian J. Lasky, Ph.D. was Chief until he joined the Peace Corps in 1962. At that point, C. James Klett, Ph.D., assumed leadership of CNPRL. Klett continued as Chief for the balance of its existence as the CNPRL and thereafter as a Cooperative Studies Program Coordinating Center. Klett had been recruited to CNPRL shortly after Holsopple's unexpected death. He was a young research and clinical psychologist from Northampton (Mass.) VA Hospital, who had interviewed patients for the lobotomy study during his internship at the American Lake (Wash.) VA Hospital.

Figure 8.5. James Klett, Ph.D.

Organization of the studies and of the CNPRL

The CNPRL quickly developed an organizational structure to design and implement cooperative trials. Early on, it acquired its own statistical staff, which often worked in collaboration with university consultants. The group of VA consultants who conceived the first study remained as an advisory committee, at first informal and later as a formal Executive Committee. Eugene Caffey, Jr., M.D., then a Staff Psychiatrist at Perry Point hospital, served on this committee from the beginning and remained on it after he moved to Central Office as Deputy Assistant Chief Medical Director for Professional Services. He and Hollister both served through the Executive Committee's entire 20-year history. The current Director of Neuropsychiatry Service in Central Office, or its successor Services, was always on the Executive Committee and was deeply involved in the planning and execution of studies, even after the CNPRL and its studies officially joined the Research Service in 1962. Most other Executive Committee members served for shorter terms. They represented many interests and disciplines and made important contributions to the success of the program.

Figure 8.6. The Executive Committee in 1966

How a study was created

Generally, the Executive Committee originated and approved the concept of a study in collaboration with the CNPRL staff. After concept approval, staff developed the complete protocol, which the Executive Committee would review. Once approved, the new study with its protocol would be announced in a letter sent to all VA psychiatric hospitals and others with large psychiatric patient populations. Participants were chosen from hospitals that expressed an interest in the study. The test drugs or placebos were furnished to the participants, but the only other tangible reward for study cooperation was attendance at the annual conference.

Starting with the second annual meeting, pharmaceutical firm representatives were invited to attend. The drug companies provided study drugs and matching placebos without cost, and sometimes they helped with packaging. Otherwise, they did not fund the CNPRL-sponsored studies, nor did they dictate or approve the study design.

CNPRL staff designed protocols, recruited participating hospitals, received data, analyzed results, planned the annual meetings of participants and generally nourished the program. As new methodologies were needed, they saw to it that they were developed. When it was time to publish results, they often wrote the papers. This was a different process from the simultaneous VA cooperative studies in medicine and surgery, which usually were initiated and designed by the field investigators who carried them out, assisted by biostatisticians from Central Office. It also differed from the present-day Cooperative Studies Program (Chapter 18), in which planning originates with staff members in the medical centers but is completed collaboratively together with one of the Cooperative Studies Program (CSP) Coordinating Centers.

There was active collaboration between the CNPRL and Dr. Lorr's laboratory in developing psychiatric rating scales and in research directed toward defining psychiatric syndromes by factor analysis and clustering techniques. In addition, psychologists in the CNPRL worked on evaluation scales. John Overall, Ph.D., was a member of the CNPRL staff from 1959 to 1961, having joined after a postdoctoral fellowship in psychometrics. When he arrived, data from the third cooperative study, a comparison of six phenothiazine derivatives, was just coming in. He and Donald Gorham, Ph.D., an older psychologist with a wealth of clinical experience, worked to simplify the Lorr MSRPP, using factor analysis of the MSRPP data from the third study. This involved laborious computer work, entering all of the data onto punched cards and waiting three months while a commercial computer firm programmed a matrix analysis, since VA had no computers available for research at that time.[19] Eventually, combining Overall's knowledge of factor analysis and Gorham's clinical understanding, they produced the Brief Psychiatric Rating Scale (BPRS),[20] which is still in widespread use in psychiatric research.

Later studies sponsored by the CNPRL

The landmark chlorpromazine study was followed by a sequence of studies evaluating all the important antipsychotic drugs available at that time.[17, 21, 22] The cooperative group studied effects of different dosage schedules and "drug holidays" or even complete discontinuation of treatment.[23] They studied psychotherapy as an adjunct to or substitute for neuroleptic medication[24] and evaluated the long-term need for anti-Parkinson drugs by chronic patients.[25]

For a number of years, Dr. Lorr and others studied the use of minor tranquilizers and psychotherapy in treatment of neurotic patients. These studies[26] were shared with the Executive Committee of the CNPRL.

The CNPRL also undertook some of the earliest investigations of antidepressant drugs. In 1954, Geigy Pharmaceuticals synthesized the first effective tricyclic antidepressant, imipramine. But the drug's antidepressant effects became recognized only in the late 1950s. VA researchers and clinicians saw the need to evaluate this class of drugs as well as the phenothiazines. A study comparing imipramine with isocarboxazid, amobarbital-dextroamphetamine and placebo showed

the efficacy of imipramine but was confounded by the high rate of spontaneous improvement in all groups.[27]

In the late 1960s and 1970s, the CNPRL began branching out beyond its earlier focus on phenothiazines and antidepressant medications. Around 1961, Samuel C. Kaim, M.D., came to Central Office Research Service as Program Chief in Psychiatry. He was especially interested in addictive disorders and sparked studies on alcoholism and drug abuse. Noteworthy was a double-blind study of 537 patients undergoing alcohol withdrawal that compared chlordiazepoxide, chlorpromazine, hydroxyzine, thiamine and a placebo, given for a 10-day detoxification period. As to general symptomatic improvement, no significant differences were found among treatments, but chlordiazepoxide (Librium) was clearly the most effective of the drugs studied for prevention of delirium tremens and convulsions.[28] In the late 1960s and early 1970s, VA collaborated with the Special Action Office for Drug Abuse Prevention (SAODAP), an interagency group under the White House, in a study comparing a long-acting methadone analog, L-alpha-acetyl methadol, with two dosage levels of methadone in the treatment of heroin addicts. The new drug, administered three times a week, was as safe as daily methadone and compared favorably with high-dose methadone in efficacy.[29] The superiority of high-dose methadone over low doses in this study contributed to the ongoing controversy about appropriate maintenance dose. Several subsequent studies showed additional evidence of safety and efficacy of L-alpha-acetyl-methadol as well as guidance for induction and crossover schedules.

In the late 1960s,Dr. Jonathan Cole, who by this time was head of the Psychopharmacology Center at the National Institute of Mental Health (NIMH), invited CNPRL to submit a grant application on the role of lithium in the treatment of manic-depressive disorders and schizophrenia in 12 VA hospitals and six public hospitals. Dr. Caffey was designated as principal investigator. This jointly funded VA-NIMH study was reviewed by both agencies, coordinated by CNPRL and overseen by a joint Executive Committee chaired by Caffey. At the suggestion of the NIMH review committee, additional funds were provided to support a new position for an assistant at the CNPRL. Robert F. Prien, Ph.D., was recruited to the CNPRL and assumed essentially all responsibility for the study in both VA and non-VA hospitals. The study evaluated lithium compared with other active therapies in the affective disorders,[30] as prophylaxis against recurrence,[31] and for treatment of patients with schizoaffective disorder in the excited state.[32] Unlike other studies coordinated by the CNPRL, hospitals that collaborated in the lithium studies were funded. NIMH paid for the extra staffing and other expenses required by the study.[33]

Annual Research Conference on Chemotherapy in Psychiatry

These studies were enhanced by annual conferences that had an important effect on the morale of the participants. In April 1956, the Central Office Psychiatry and Neurology Service sponsored the first such conference at the Downey (Ill.) VA Hospital. Some 75 people attended, including representatives from VA neuropsychiatric hospitals and other VA hospitals with large psychiatric sections. CPNRL staff and key people from Central Office were also present.[34] This meeting became an annual event for 20 years. At the second meeting, 17 representatives of 10 pharmaceutical firms were among the more than 100 attendees.[35]

The Neuropsychiatry Service coordinated the annual meetings. They fostered cooperation between the hospitals and participating disciplines and catalyzed friendships among people from various hospitals and with Central Office and CNPRL staff. The social aspects were also important. Psychiatrists, psychologists, nurses, social workers and statisticians attended and participated. Clyde Lindley, the Administrative Officer for Neuropsychiatry Service, encouraged the studies and secured funding for the conference each year. He and others maintained a high standard for the scientific presentations that soon became the dominating feature of the conference.[36]

The flavor of these meetings is reflected in a description in the May 1961 *Research and Education Newsletter*:

> "About 250 scientists attended the Sixth Annual Conference of the VA Chemotherapy Studies in Psychiatry and Broad Research Approaches to Mental Illness, held at the Netherlands Hilton Hotel, Cincinnati, Ohio, March 27-29, 1961 ... The Chief Medical Director, Dr. William S. Middleton, opened the conference with a brief address. Invited addresses were delivered by Dr. Carrol Keonig, VAH Chicago (Res), Illinois, Dr. R.G. Kuhlen, Syracuse University and Dr. J. T. Shurley, VAH, Oklahoma City, Oklahoma.
>
> "There were preliminary reports on the VA's Cooperative Study No. 5, Chemotherapy of Depression, and Study No. 6, an evaluation of several drugs in treating newly admitted schizophrenic patients. The NIMH made a preliminary report on a 9-hospital collaborative study evaluating drugs in treating acute schizophrenic patients. An initial report was made on the VA Cooperative Study with Psychiatry Outpatients, evaluating the effectiveness of early treatment with a tranquilizer. Thirty research papers were presented which covered a wide range of topics in the field of mental illness, from the neurophysiological to the effect of milieu therapy. Four symposia were presented to highlight significant research approaches to the field of mental illness."

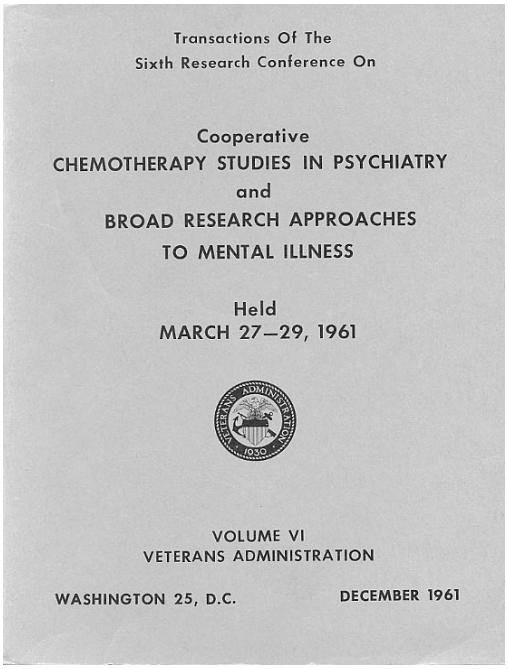


Figure 8.7. Published Proceedings of the annual conferences

In addition to VA attendees, representatives were present from the American Psychiatric Association, the Mental Health Institute at the University of Michigan, the New York Department of Mental Health and NIMH.[37]

These annual conferences, with name changes to reflect their increasingly broader scope, continued through the 20th annual conference in April 1975, held shortly before Clyde Lindley retired from VA[38] and when the CNPRL was transferring its operations to the Cooperative Studies Program. That meeting had nearly 600 participants, offered CME credit, and covered such diverse topics as biofeedback, family therapy, suicide prevention and drug abuse, as well as the cooperative studies program.[39]

Impact of the CNPRL studies

These studies had broad impact, even beyond proving the efficacy of drug treatment for psychiatric disorders, The centrally directed program brought psychiatrists and many additional physicians into research. The studies' tests and scales became widely used in VA and elsewhere. For example, the NIMH adopted the BPRS as part of the standard assessment battery in its Early Clinical Drug Evaluation Unit. Spin-off research projects were begun in hospitals where staff previously had little motivation or opportunity to carry out research. Dr. John Barnwell, who started the tuberculosis trials, said when he addressed the members of the first conference of this cooperative group in 1956:

> "When you bring together a considerable number of doctors into a cooperative study, you obviously gather a group of individuals of varying experiences and capacities. As with many graduates of medicine, some have never before participated in any investigation. Some have

never distinguished between observed fact and the professor's opinion. A well-conducted cooperative study forces all to attempt to make this distinction and it helps us all to clarify and identify our problems. It may make investigators out of some who never realized that the body of medical knowledge was a growing, living thing with its own diseases and relapses."[40]

CNPRL-coordinated studies involved many VA staff who otherwise would not have participated in research. Some who entered research through this program were later successful in their own research programs. Especially in the early days, the major motivation for hospital psychiatrists to take part in these trials was altruistic. They received little or no reward for participation. Some were invited to the annual study meetings, but few became authors of the resulting scientific papers. Their main reward was sharing the excitement of being part of an important venture to help patients. This opportunity was particularly important to those working in isolated, unaffiliated hospitals.

In 1972, when Cooperative Studies Program Coordinating Centers (CSPCCs) were set up to manage the administrative and statistical aspects of the cooperative studies (Chapter 18), a new CSPCC was established at Perry Point with Dr. Klett as its Chief. The CNPRL continued as a separate entity, with Klett remaining as its chief until 1975. During this time, Dr. Prien completed the lithium studies and prepared several review papers. One important product is a 1975 monograph, an annotated program bibliography of publications from the two decades of the CNPRL existence.[26] Thereafter, new cooperative studies were handled by the Perry Point CSPCC. At first, this new CSPCC concentrated on neuropsychiatric protocols, but gradually it took on studies in other subject areas and soon entered the mainstream of the Cooperative Studies Program.

Impact of the VA psychopharmacology studies on psychiatry

Psychiatric science and practice have undergone enormous change since the 1950s. One of the most significant developments in psychiatry was the creation of VA multi-center cooperative studies for evaluation of psychiatric interventions described in this chapter. The basis of psychiatric clinical practice has moved from relying mostly on individual, expert judgment to learning from rigorous outcome studies. VA has continued to sponsor Cooperative Studies directed at improving the treatment of its patients with serious mental illnesses. In recent years, VA psychopharmacology cooperative studies have included the recent generations of new antipsychotic drugs.

A major outcome of the VA studies, and of similar studies by others, was a massive exodus of psychiatric patients from state and federal institutions, the most dramatic change in American psychiatry over the last half of the 20th century. From the mid-19th century until the 1950s, the number of patients in psychiatric hospitals continually rose. At the 1955 peak, 559,000 individuals resided in state hospitals. VA institutions experienced similarly high growth in numbers of residential psychiatric patients (Figure 8.1). In the 1950s, psychiatric patients constituted nearly 60 percent of the VA patient population. Some 40 years later, by 1997, the number of patients in state hospitals plummeted to 62,722, although the U.S. population had nearly doubled since the mid 1950s.[41] VA's inpatient psychiatric population has declined in parallel. The savings in cost and suffering made possible by the proper use of psychoactive drugs is immeasurable. The studies described in this chapter expedited and legitimized their use.

Acknowledgment: Joel Braslow, M.D., Ph.D., made important contributions to this chapter.

References

1. Braslow, J., *Mental Ills and Bodily Cures: Psychiatric Treatment in the First Half of the Twentieth Century.* Berkeley: University of California Press, 1997.

2. Swazey, J.P., *Chlorpromazine in Psychiatry: A Study of Therapeutic Innovation.* Cambridge, MA: MIT Press, 1974.

3. Ayd, F.J., "The Early History of Modern Psychophysiology. 29th (1990) Annual Meeting of the American College of Neuropsychopharmacology, San Juan, PR." *Neuropsychopharmacology*, 1991. **5**: 71-84.

4. Healy, D., *The Antidepressant Era*. Cambridge, MA: Harvard University Press, 1997.

5. Valenstein, E.S., *Great and Desperate Cures: The Rise and Decline of Psychosurgery and Other Radical Treatments for Mental Illness.* New York: Basic Books, 1986.

6. Appel, K., Myers, J.M. and Scheflen, A.E., "Prognosis in psychiatry: Results of psychiatric treatment." *Arch Neur Psychiatry*, 1953. **70**: 459-468.

7. Barahal, H.S., "1000 prefrontal lobotomies - a five-to-10-year follow-up study." *Psychiat Quarterly*, 1958. **32**: 653-678.

8. Robin, A.A., "A controlled study of the effects of leucotomy." *J Neurol, Neurosurg and Psychiatry*, 1958. **21**: 262-269.

9. *Psychopharmacology: Problems in Evaluation.* Cole, J.O. and Gerard, R.W., eds.; Washington, DC: National Academy of Sciences, 1959.

10. Barsa, J.A., "The fallacy of the 'double blind'." *Am J Psychiatry*, 1963. **119**: 1174-1175.

11. Jenkins, R.L. "Intra-VA research in neurology and psychiatry." *25th meeting of the Committee on Veterans Medical Problems*. December 5, 1952. Washington, DC: National Academy of Sciences-National Research Council, Appendix IV.

12. Pressman, J.D., *Last Resort: Psychosurgery and the Limits of Medicine*. Cambridge, New York, Melbourne: Cambridge University Press, 1998, 394-397.

13. Ball, J., Klett, C.J. and Gresock, C.J., "The Veterans Administration study of prefrontal lobotomy." *J Clin Exptl Psychopathology and Quarterly Rev Psychiatr Neurol*, 1959. **20**: 205-217.

14. Lindley, C.J. "VA hospital survey of tranquilizing drugs." *Second Research Conference on Chemotherapy in Psychiatry*. Downey, IL: Office of the Chief Medical Director, Veterans Administration, Washington, DC, 29-30.

15. Interview with Leo E.Hollister, M.D., January 29, 1994 at his residence in Houston, TX.

16. Hollister, L.E., Krieger, G.E., Kringel, A. and Roberts, R.H., "Treatment of chronic schizophrenic reactions with reserpine." *Ann NY Acad Sci*, 1955. **61**: 92-100.

17. Casey, J.F., Bennett, I.F., Lindley, C.J., Hollister, L.E., Gordon, M.E. and Springer, N.N., "Drug therapy in schizophrenia: A controlled study of the relative effectiveness of chlorpromazine, promazine, phenobarbital, and placebo." *Arch Gen Psychiat*, 1960. **2**: 210-220.

18. Hollister, L.E. "Discussion, first plenary session." *Second Research Conference on Chemotherapy in Psychiatry*. May 9-10, 1957. Downey, IL: Office of the Chief Medical Director, Veterans Administration, Washington, DC, 25-26.

19. Interview with John Overall, Ph.D., January 28, 1994 at Dr. Overall's office in Houston, TX.

20. Overall, J.E. and Gorham, D.R., "The Brief Psychiatric Rating Scale." *Psychol Rpts*, 1962. **10**: 799-812.

21. Casey, J.F., Hollister, L.E., Klett, C.J., Lasky, J.J. and Caffey, E.M., Jr., "Combined drug therapy of chronic schizophrenics: A controlled evaluation of placebo, dextroamphetamine, imipramine, isocarboxazid, and trifluoperazine added to maintenance doses of chlorpromazine." *Amer J Psychiat*, 1961. **117**: 997-1003.

22. Lasky, J.J., Klett, C.J., Caffey, E.M., Jr., Bennett, J.L., Rosenblum, M.P. and Hollister, L.E., "Drug therapy of chronic schizophrenics: A comparative evaluation of chlorpromazine, chlorprothixene, fluphenazine, reserpine, thioridazine, and triflupromazine." *Dis Nerv Syst*, 1962. **23**: 698-706.

23. Caffey, E.M., Jr., Diamond, L.S., Frank, T.V., Grasberger, J.C., Herman, L., Klett, C.J. and Rothstein, C., "Discontinuation or reduction of chemotherapy in chronic schizophrenics." *J Chron Dis*, 1964. **17**: 347-358.

24. Gorham, D.R., Pokorney, A.D. and Moseley, E.C., "Effects of phenothiazine and/or group psychotherapy with schizophrenics." *Dis Nerv Syst*, 1964. **25**: 77-86.

25. Klett, C.J. and Caffey, E.M., Jr., "Evaluating the long-term need for antiparkinson drugs for chronic schizophrenics." *Arch Gen Psychiat*, 1972. **26**: 374-376.

26. Abrams, S. and Ciufo, S., *Cooperative Studies in Mental Health and Behavioral Sciences*. Washington, DC: Department of Medicine and Surgery, Veterans Administration, 1975, ii.

27. Overall, J.E., Hollister, L.E., Pokorney, A.D., Casey, J.F. and Katz, G., "Drug therapy in depressions: Controlled evaluations of imipramine, isocarboxazid, dextroamphetamine-amobarbital, and placebo." *Clin Pharmacol Therapeut*, 1962. **3**: 16-22.

28. Klett, C.J., Hollister, L.E., Caffey, E.M., Jr. and Kaim, S.C., "Evaluating changes in symptoms during acute alcohol withdrawal." *Arch Gen Psychiat*, 1971. **24**: 174-178.

29. Ling, W., Charavastra, C., Kaim, S.C. and Klett, C.J., "Methadyl acetate and methadone as maintenance treatments for heroin addicts." *Arch Gen Psychiat*, 1976. **33**: 709-720.

30. Prien, R.F., Caffey, E.M., Jr. and Klett, C., J, "Comparison of lithium carbonate and chlorpromazine in the treatment of mania." *Arch Gen Psychiat*, 1972. **26**: 146-153.

31. Prien, R.F., Caffey, E.M., Jr. and Klett, C., J, "Factors associated with treatment success in lithium carbonate prophylaxis." *Arch Gen Psychiat*, 1974. **31**: 189-192.

32. Prien, R.F., Caffey, E.M., Jr. and Klett, C., J, "A comparison of lithium carbonate and chlorpromazine in the treatment of excited schizo-affectives." *Arch Gen Psychiat*, 1972. **27**: 182-189.

33. Interview with C. James Klett, Ph.D., January 11,1990 at a hotel lobby in Washington, D.C.

34. *First Research Conference on Chemotherapy in Psychiatry*. Downey, IL: Office of the Chief Medical Director, Veterans Administration, Washington, DC, 1956.

35. *Second Research Conference on Chemotherapy in Psychiatry*. Downey, IL: Office of the Chief Medical Director, Veterans Administration, Washington, DC, 1957.

36. Telephone interview with C. James Klett, Ph.D., March 12, 2001.

37. Kaim, S. and Lindley, C., *R&E Newsletter*, May, 1961, 14-15.

38. Klett, C.J. "Preface." *Highlights of the 20th Annual Conference, Veterans Administration Studies in Mental Health and Behavioral Sciences*, i.

39. *Highlights of the 20th Annual Conference, Veterans Administration Studies in Mental Health and Behavioral Sciences*. Klett, C.J., ed. Perry Point, MD: Veterans Administration, 1975,

40. Barnwell, J.B. "The value of cooperative research." *First Research Conference on Chemotherapy in Psychiatry*. Downey, IL: Office of the Chief Medical Director, Veterans Administration, Washington, DC, 3-5.

41. Lamb, H.R., "Deinstitutionalization and public policy", in *American Psychiatry after World War II (1944-1994)*, Menninger, R.W. and Nemiah, J.C., Editors. 2000, American Psychiatric Press: Washington, DC 259.

(this page left intentionally blank)

Chapter 9. The Hypertension Studies

The relationship between hypertension, commonly referred to as high blood pressure, and adverse health effects has long been recognized. People with hypertension are more likely than others to have cardiovascular disease, heart attacks, stroke and heart failure. VA medical research over more than 60 years has significantly contributed to the improved treatment of hypertension.

In their 1948 review of young service men who had heart attacks during World War II, Wallace M. Yater, M.D., and his colleagues at the Washington (D.C.) VA Hospital showed that enlistment blood pressures in men who had coronary attacks were higher compared with those of men who were later treated by VA for amputations.[1] These authors reviewed earlier publications that also showed this effect. While the relationship between hypertension and vascular disease was already well established, it was by no means accepted that one led to the other. Many authorities thought that hypertension and vascular disease were simply different expressions of a common problem. Unless hypertension was causing obvious problems, such as the convulsions of eclampsia in pregnancy or the headaches and papilledema of malignant hypertension, hypertension was not widely believed to require treatment.

Early treatment of hypertension

Before effective drugs became available to lower blood pressure, other approaches were recommended in standard medical textbooks. The 1925 10th edition of Osler's *Principles and Practice of Medicine*, revised by Thomas McRae, M.D., states that one should look for a correctable cause for hypertension. If no cause was found:

> "Any focus of infection should be removed... Mental rest and quiet, so far as can be secured, are important. Long hours of physical rest are useful. Exercise, short of fatigue, is helpful, best in the form of walking, golf, etc. A good vacation, often one spent at one of the springs, is an advantage. One day a week in bed on a low diet is useful in more advanced cases.
>
> "... Bathing in tepid or warm water usually is best. The bowels should be kept well open, for which a saline before breakfast is often useful. A weekly dose of blue mass or mercury and chalk powder at bedtime for two successive nights is often beneficial. Some patients do well with irrigations of the colon once or twice a week in addition."[2]

This advice had not changed much by the 1947 16th edition of the same text, revised by Henry A. Christian, A.M., M.D., LL. D. Dr. Christian advised, however, that: "The bowels should be kept normal; the oft advised free catharsis seems to the present author inadvisable." He went on to state that "A sedative, such as phenobarbital, generally is helpful."[3]

Edward Freis, M.D., of the Washington VA Hospital, whose later work was prominent in solving the hypertension problem, described the situation in 1951. He advised treating only patients with such severe hypertension that they were "almost certain to develop fatal complications within a few years." These were:

"1. Patients with hemorrhages, exudates and/or papilledema in the optic fundi.
2. Patients with diastolic blood pressures persistently above 120 mm. Hg. even after forty-eight hours of bed rest in the hospital.
3. Patients with repeated attacks of acute hypertensive encephalopathy associated with extreme elevations of blood pressure."[4]

The reason for this conservatism was that while the available effective treatments—surgical sympathectomy, Walter Kempner. M.D.'s "200 mg sodium diet"—a diet of rice, fruit, sugar and iron supplements low in fat and in sodium--and toxic drugs—could be life-saving, they were very hard on the patient. Freis and others searched for effective, less toxic drugs to lower blood pressure, and within the next few years the search began to produce results.

Should hypertension be treated?

By the 1950s and 1960s, effective drugs for reducing blood pressure were becoming available. Mortality in patients with malignant hypertension who were treated with the new drugs was shown to be markedly reduced when compared to historical controls.[5] Increasing numbers of cardiologists favored drug treatment for severe or malignant hypertension.[6] But even that opinion was not universal, and there was no agreement about the best way to handle less severe cases, patients with diastolic blood pressures under 120 mm Hg.

Even though cardiology texts started advising drug therapy for severe hypertension, standard medical textbooks generally hesitated to advise drug therapy. For example, a 1966 British textbook of medicine stated:

"In the present status of therapy there is no justification in attempting to lower the blood pressure by drugs or operation in the absence of symptoms. An exception might be made in young subjects, especially men, with a high fixed level of blood pressure (e.g. diastolic exceeding 120 mm.). In such cases it may be felt that complications are likely to occur sooner rather than later and for this reason some reduction of the pressure with hypotensive drugs is justifiable. The level may be regarded as fixed when residual hypertension persists after 7 days' complete rest in bed with adequate sedation."[7]

The 1967 edition of the *Cecil and Loeb Textbook of Medicine*, contained the following "philosophy of treatment":

"Be sure that the patient really needs treatment. Those over 70 years rarely do, whatever the level of pressure, and certainly should not be treated unless a definite indication such as pulmonary edema, angina pectoris, severe headache or marked shortness of breath on effort is present. It is sad to see a well preserved patient of 70 years with an arterial pressure of 190 systolic, 90 diastolic in mm. of mercury due to the presence of a rigid aorta receiving treatment for a headache or other symptoms that are manifestations of anxiety or depression. Age needs no additional therapeutic hazards."[8]

A 1966 book, *Controversy in Internal Medicine*, included a strongly stated criticism of those who treated even severe hypertension. Hypertension researchers William Goldring, M.D. and Herbert

Chassis, M.D. stated, "We believe that we are now in an era of empiric treatment of hypertension, in which a huge uncontrolled clinical-pharmacological experiment may be masquerading as a clinically acceptable therapy." They commented:

> "The effect of artificially lowered blood pressure on the occurrence of cerebral vascular accidents and myocardial infarction or failure has been reported, but only as a statistical relationship between these complications and the level of blood pressure. . . . Furthermore, there are sufficient reports in the literature indicating that coronary disease may progress in spite of artificially lowered blood pressure."

They even questioned the value of lowering blood pressure in "accelerated hypertension" or "malignant hypertension," concluding that:

> "After about 15 years of data collecting, we believe that the alleged usefulness of antihypertensive drugs rests on conclusions drawn from notoriously uncertain statistical compilations compounded by equally uncertain estimates of morbidity and mortality in the natural history of a disease of highly unpredictable course."[9]

Two other papers in the same book[10, 11] placed more value on use of antihypertensive drugs. In his summarizing "Comments," Arnold Relman, M.D., a Harvard Medical School professor who later on became the editor of the New England Journal of Medicine asks: "It is not difficult in most cases to lower blood pressure with various types of drugs, but does this prolong life or prevent serious cardiovascular complications?" His perspective was that:

> "We need more controlled prospective studies. I suspect, however, that few will be forthcoming, so that the practicing physician is faced with a familiar dilemma."

Relman concluded:

> "If he is prudent, I believe he will reserve drug therapy—for only those patients with moderate or severe hypertension whose blood pressures cannot be improved by simpler measures. While using drugs, the physician must be aware of the possible dangers of long-range toxic effects and of all the uncertainties implicit in the uncontrolled experiment he is conducting."[12]

To find answers to the questions and address skepticism about hypertension treatment, in 1956 Dr. Edward Freis, Chief of the Medical Service at the Washington VA Hospital, assembled a group of colleagues from other VA facilities to start a cooperative study on antihypertensive drugs.

Edward D. Freis, M.D.

Freis, interested in research since childhood, published several clinical papers during his early medical training. While in an Air Force pathology laboratory in Lincoln, Neb., during World War II, he worked with I. Arthur Mirsky, M.D., who was already famous for his diabetes research. Mirsky shared a tremendous enthusiasm for research and taught Freis much about how to carry out medical investigation.[13] Together, they published a paper on shock induced by trypsin.[14]

Figure 9.1. Edward Freis, M.D.

After the war, Freis returned to Boston University to complete his residency under Chester S. Keefer, M.D. Keefer introduced him to James Shannon, of later importance to the NIH, who was then head of the Squibb Institute for Medical Research. Shannon wanted to study the chemotherapy of hypertension. His previous search for antihypertensives, which had not been successful, included work on the red pigment in lobster shells, since the Russians had reported that ground-up lobster shells reduced blood pressure.

Now, Shannon wanted to test pentaquine, an antimalarial drug used during World War II, which caused hypotension when given in large doses. Freis agreed to do the clinical trials. The hospital assigned a wing of a ward for a clinical trial of pentaquine in hypertensive patients. The drug produced severe side effects, but it did lower blood pressure and help some patients with the most severe hypertension.[15]

After that, Freis and his fellow resident Joseph Stanton, M.D., learned about veratrum viride from a review paper by Otto Krayer, M.D., of Harvard.[16] Veratrum viride had been used by American Indians in their initiation rites to cause vomiting and collapse as well as by 19th century physicians in Appalachia to treat eclampsia. Freis and Stanton studied it in their hypertensive patients. They found the therapeutic window was very narrow: The dose that lowered the blood pressure often caused bradycardia, sweating and projectile vomiting. They found the drug's effectiveness improved by combining it with a low-sodium diet. They followed up with a series of other studies of drugs having some benefit to patients with severe hypertension.

In 1949, Freis was recruited to Washington, D.C., to be Assistant Chief of the Medical Service at the Washington VA Hospital and a faculty member at Georgetown University. At first his laboratory was primarily at Georgetown, but he gradually moved his base of operations to VA. He found that VA patients were more cooperative in his clinical research than Georgetown clinic patients. Also, VA had a good laboratory, partly in the same facility as the old Cardiovascular Research Laboratory that closed in 1949 (Chapter 2). There, Freis conducted hemodynamic studies, primarily on cardiac patients. An important product of this period of research was the demonstration that cardiac output and stroke volume decreased in proportion to the severity of myocardial infarction. He worked with engineers from the National Bureau of Standards to develop the first monitoring equipment and other special equipment for cardiac patients.

All along, Freis continued his clinical research on drugs to counteract hypertension. The most important breakthrough, in 1957, was the development of chlorothiazide, a new diuretic drug that quickly supplanted injection of mercurial diuretics in edematous patients. Freis had tried mercurials in severe hypertension and saw the potential of chlorothiazide therapy for hypertension. He quickly treated a series of hypertensive patients with this new drug and presented his results at the next meeting of the American Heart Association.

Beginnings of the VA cooperative studies on hypertension

Freis learned about the cooperative study approach to clinical research in the early 1950s. During a meeting of cardiologists in Europe, Freis joined a VA colleague, Hubert V. Pipberger, M.D., in a visit to Paul Martini, M.D., a well-known medical statistician in Germany. Together, they discussed Pipberger's interest in cooperative studies in vectorcardiography. Returning to the conference, Freis defended his use of drug treatment for hypertension and encountered opposition to his position. He concluded that his only alternative was to use multi-clinic trials in the fashion he and Pipberger had discussed with Martini.

At a VA Chiefs of Medicine meeting, Freis gained the interest of about 15 people in mapping out a plan to conduct such a study. His original thought was for a "very simple design—placebo versus treatment—the best treatment you had available at the time—and follow up for complications." But, everyone wanted to add to it. Freis described what he encountered:

> "The plan was made out by the doctors. There was no help yet at that stage from any statisticians, and it was a lousy plan.... Pretty soon it was loaded.... We were comparing different drugs at the same time we were studying effectiveness and mortality. Well, we learned after that that you can't have two main objectives in the same study."

Freis took the group's plan to VA Central Office. In a Nov. 26, 1956, press release, the goal of the study was described as "determining how well newer drugs control high blood pressure and whether they can prevent hardening of the arteries, heart attacks, strokes and other complications of the disease."[17] The leaders in the cooperating VA hospitals, in addition to Freis, were Mark Armstrong, M.D., and Walter Kirkendall, M.D., of Iowa City, John Bakke, M.D., and Harold Dodge, M.D., of Seattle, Massimo Calebresi, M.D., of West Haven (Conn.), Loyal Conrad, M.D., of Oklahoma City, E.E. Eddelman, M.D., of Birmingham (Ala.), Rudolph Fremont, M.D., of Brooklyn (N.Y.), David Littman, M.D., of West Roxbury (Mass.), Clifford Pilz, M.D., of Chicago West Side, Eli Ramirez, M.D., of San Juan (Puerto Rico) and David Richardson, M.D., of Richmond (Va.).

Results of the first series of studies by this group of investigators were reported in a series of papers in the *Annals of Internal Medicine* between 1960 and 1962.[18-20] These studies helped to establish the most effective ways to control hypertension using then-available agents, but they did not answer the central question of whether this led to prevention of the disease's complications.

Resolving hypertension's core question

In 1963, Freis and a group of investigators from earlier studies planned a study specifically designed to resolve the essential mystery surrounding hypertension treatment. This time, they

planned closely with Lawrence Shaw, A.M.,[21] the new head of research biostatistics at VA Central Office to keep the study design simple. From their work on available drugs, they chose what they considered to be the best regimen, a combination of hydrochlorothiazide, reserpine and hydralazine. They persuaded the pharmaceutical companies to provide placebo tablets. Additional special tablets, each with its own placebo, were available when doses of one or another drug needed to be adjusted because of side effects.

Patients were very carefully selected for this study. Veterans with hypertension were hospitalized for an initial workup before enrollment. Those whose diastolic blood pressures averaged between 90 and 129 mm Hg during days four through six of a hospital stay were considered for the study. They selected only patients who appeared motivated and had no existing severe hypertensive sequelae. As Freis recalled, although there was no formal consent process, the patient's preference to return to his usual practitioner was a formal basis for exclusion.

The investigators rigorously checked a patient's reliability before accepting him into the study. After hospital discharge and before randomization, patients received two placebo tablets, one containing riboflavin. During two subsequent clinic visits, pill counts were done and urine was checked by fluorescence for riboflavin content. Excluded from the study were patients who failed to keep both appointments and bring their pills, had incorrect pill counts, or had no riboflavin in their urine. With these precautions, noncompliance—probably the most important cause of treatment failure in ordinary practice—could be minimized.

This study began in April 1964 and only the statistical staff were aware of the results until they were "unblinded" in 1969. However, in early 1967, Shaw told Freis of his early analysis of results from patients with severe hypertension, defined as diastolic pressures 115 through 129. By this time, 143 patients with severe hypertension were enrolled in the study, 70 of them on placebo medication. Fifty-five patients with severe hypertension, 23 on placebo, had been followed for more than two years. Analyzing this group of patients, Shaw found that the number of serious cardiovascular events was much greater in the placebo group, showing a convincing degree of statistical significance. Serious cardiovascular "events" had occurred in 27 of the placebo-treated severely hypertensive patients but in only two of those receiving active antihypertensive treatment. There was no question that reducing a markedly elevated diastolic blood pressure helped to protect the patient. Patients in this "severe hypertension" group were immediately dropped from the study, and those who had been on placebo received active treatment to reduce their blood pressures.

The *Journal of the American Medical Association* published the results in December 1967.[22] As Freis recalled, this paper on treatment of severe hypertension didn't cause much discussion. But he also recalls deciding against having a press release. Just as there were those who still needed to be convinced that treatment of hypertension is efficacious, there were others, convinced that lowering blood pressure protected patients, who criticized the group for doing a placebo-controlled study. And the more difficult question—whether treatment of mild and moderate hypertension is efficacious—still needed to be answered.

So the group continued to enroll patients with diastolic pressures up to 114 for another two years, until September 1968. The "blind" for these patients continued until after the last observations had been completed in October 1969. Three hundred eighty patients had been observed for one to five years, on average for more than three years.

As before, throughout the course of the study, the statistical group continued to monitor the "unblinded" data. They shared the results with Central Office officials. One Saturday in October 1969, Thomas Chalmers, M.D., Assistant Chief Medical Director for Research and Education and an authority on controlled clinical trials, was working at his desk in Central Office. He looked at the latest statistical analysis of results from the hypertension study. It was clear that reducing blood pressure prevented stroke and congestive heart failure. Immediately, Chalmers sent out instructions to the study clinics to put all patients on active treatment and to break the blind. Later, the group found that the significance of their findings was primarily due to the patients with moderate hypertension, diastolic pressures 105-114. It would take a later, much larger, study to prove the protective effect of treating even mild hypertension.

This VA report, by virtue of its randomized, double-blind, placebo-controlled design, presented the first definitive and convincing proof that treating moderate hypertension was beneficial in preventing or delaying many of its catastrophic health complications.

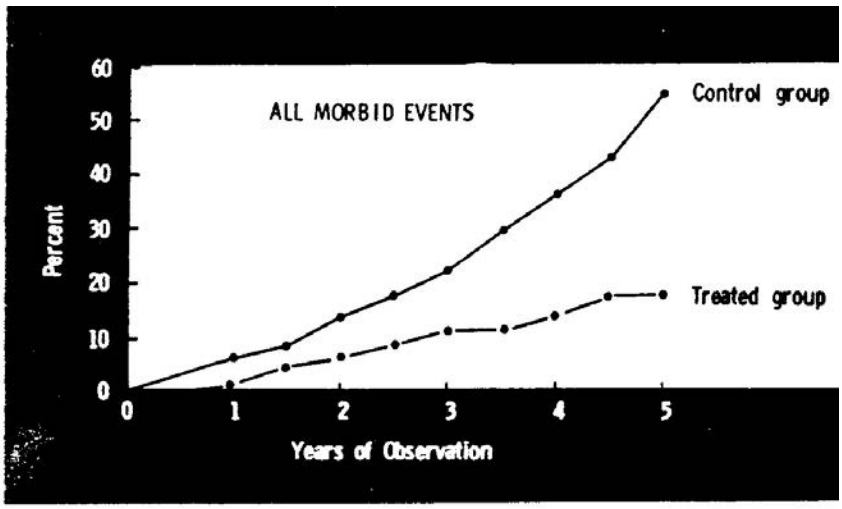


Figure 9.2. Results of the study of patients with moderate hypertension

Response to the study

The report of the study showing the efficacy of treatment of moderate hypertension appeared in *JAMA* in August 1970.[23] It provoked little immediate reaction. The Associated Press circulated the news, but not much was published in the general press. As Freis recalled, there was little immediate interest among physicians. However, the results were recognized in the 1971 edition of the *Cecil-Loeb Textbook of Medicine*: "Now that controlled trials of treatment in less severe grades of hypertension have been carried out, it is clear that improvement in outlook is conferred by successful treatment." Nevertheless, the textbook continued to advise against treating the elderly.[24]

In May 1971, Freis spoke at a special seminar on clinical trials held by the "Young Turks" (the American Society for Clinical Investigation) at its Atlantic City meeting. Freis recalled that Mary Lasker had heard about the study and approached Secretary of Health, Education and Welfare Elliot Richardson with reprints of Freis's papers and publications. Richardson, whose physician father had had hypertension and died of a stroke, ordered the creation of a nationwide effort to publicize hypertension. This program became known as the National High Blood Pressure Education Program.

In November 1972, Freis received the Lasker Award for his contributions to clinical medicine.

The 1974 edition of *Controversies in Clinical Medicine* included a follow-up to the 1966 disagreement on the treatment of hypertension:

> "There has (in the first edition) been a difference of opinion in regard to the treatment of benign hypertension, but both Hollander and Relman stated the need for a carefully controlled prospective study. Such a study has now been done.
>
> "The results of a clinical trial conducted in the Veterans Administration and led by Freis conclusively demonstrated the value of treating patients with benign hypertension of a moderate or severe grade."[25]

Nevertheless, skepticism about benefit from treatment of hypertension waned slowly. Even in 1997, Moser wrote:[26]

> "Even as results of therapy in the 1950s and the early 1960s improved, progress was still held back by prevailing attitudes of therapeutic nihilism, popularized and given respectability by several leading medical authorities. It is hard to believe, but some experts still believed that arterial disease was the cause of the hypertension rather than the result. These opinions scoffed at the use of drug as treatment of the manometer or the 'numbers' rather than the patient. There was disbelief that benefit could be achieved by just paying attention to the numbers. In the mid 1950s at the New York Academy of Medicine, we presented 10 cases of malignant hypertension, who had experienced clearing of fundoscopic abnormalities and heart failure and as a result of blood pressure lowering. Two eminent authorities pronounced that this probably represented the 'natural history' of some patients. When reversal of LVH was demonstrated on EKG, a well-known New York City electrocardiographer sent us a note, 'Ain't nature grand.' (This electrocardiographer) expressed disbelief that cardiac hypertrophy could be reversed by just lowering the blood pressure (paying attention to the manometer). In view of more recent data, this attitude seems strange indeed.
>
> "But some hypertension experts in the 1990's still belittle the benefits of 'just lowering the blood pressure.' It may be true that modifying other risk factors in addition to lowering blood pressure will result in a greater reduction in morbidity and mortality than has been noted thus far in the clinical trials and clinical experience."

Later studies by the VA Cooperative Study Group on Antihypertensive Agents

Important questions about hypertension remained. The VA group had proven that drug treatment helped the patients they studied who had moderate to severe hypertension. These patients were relatively young, averaging about 50 years of age. How about the elderly? How about patients with mild hypertension—should they also be treated? What is the significance of systolic hypertension when the diastolic pressure is normal? How do other drugs compare with the fixed combination used in the morbidity study? Can the drugs be stopped after the blood pressure is controlled? The group of research clinicians remained together as the "Veterans Administration Cooperative Study Group on Antihypertensive Agents" and carried out a series of studies, some of them supported by the NIH and pharmaceutical companies as well as by VA.

Among their first efforts was a more detailed analysis of the data from the morbidity study on patients with mild to moderate hypertension. They found that the older the patient and the more cardiovascular or renal abnormalities present at entry, the greater the benefit from treatment. While the entry diastolic blood pressure had little effect on adverse outcomes in the treated group, treatment had a greater effect on the level of blood pressure in those with the greater entry blood pressures.[27]

In later studies, the group compared new drugs with established antihypertensive drugs in a series of carefully controlled studies.[28-35] They also studied the effectiveness of drug combinations when single drugs were not effective in sufficiently lowering blood pressure and found that combinations, especially those containing diuretics, are often effective when the same drugs given singly are not.[36] This finding has led to the recommendation that drug combinations be used routinely.[37]

A 1975 paper reporting an attempt to wean patients from antihypertensive drugs showed that only 15 percent of patients with drug-controlled hypertension remained normotensive when a placebo was substituted. However, a later study showed that dosage could frequently be reduced safely but not discontinued entirely.[38]

Following the VA group's original finding that treatment of the elderly reduced adverse events, a finding reinforced by other groups,[39-42] an NHLBI-funded study with VA participation showed that lowering systolic blood pressure below 160 mmHg in elderly persons with isolated systolic hypertension lowered the stroke rate by one-third.[40]

Implications of the hypertension studies

Proof that treatment of hypertension prevents its complications has led to widespread efforts to detect and control the condition. In 1972, anticipating that a large number of untreated hypertensive Veterans would need treatment to prevent complications, VA started the Hypertension Screening and Treatment Program (HSTP), which included 32 treatment clinics to detect and treat hypertension in Veterans. H. Mitchell Perry, M.D., of the St. Louis VA Medical Center was chairman of the program. A law change in late 1973 permitted outpatient treatment of hypertension. Treatment visits to the HSTP clinics began in January 1974 and some of these clinics are still active today. A 20-year review in 1998 showed that lowering blood pressure had been

effective in 85 percent of patients and that early treatment had decreased incidence of end-stage renal disease by half.[43]

The VA cooperative studies on hypertension have led to a revolution in the care of those with this condition. Countless people have been spared the ravages of stroke and other consequences of uncontrolled hypertension.

References

1. Yater, W.M., Traum, A.H., Brown, W.G., Fitzgerald, R.P., Geisler, M.A. and Wilcox, B.B., "Coronary artery disease in men eighteen to thirty-nine years of age." *Am Heart J,* 1948. **36**: 334-372.

2. McCrae, T., *The Principles and Practice of Medicine. Originally Written by William Osler. Tenth Edition.* New York and London: D. Appleton and Company, 1925, 864.

3. Christian, H.A., *The Principles and Practice of Medicine. Originally Written by William Osler. Sixteenth Edition.* New York and London: D. Appleton-Century Company, Incorporated, 1947, 1130.

4. Freis, E.D., "An approach to the treatment of severe essential hypertension." *Medicine Illustrated,* 1951. **5**: 53-58.

5. Perry, H.M. and Schroeder, H.A., "The effect of treatment on mortality rates in severe hypertension." *Arch Int Med,* 1958. **102**: 418-425.

6. Leishman, A.W.D., "Merits of reducing high blood-pressure." *Lancet,* 1963. **1**: 1284-1288.

7. Scott, R.B., *Price's Textbook of the Practice of Medicine*. London: Oxford University Press, 1966, 735.

8. Beeson, P.B. and McDermott, W., *Cecil-Loeb Textbook of Medicine, Twelfth Edition.* Philadelphia, London, Toronto: W.B. Saunders Company, 1967, 665-666.

9. Goldring, W. and Chasis, H., "Antihypertensive drug therapy: An appraisal", in *Controversy in Internal Medicine,* Ingelfinger, F., Relman, A., and Finland, M., Editors. 1966, W.B. Saunders Company: Philadelphia and London, 83-91.

10. Page, I.H. and Dustan, H.P., "The usefulness of drugs in the treatment of hypertension", in *Controversy in Internal Medicine*. 1966, 92-95.

11. Hollander, W., "The evaluation of antihypertensive therapy of essential hypertension", in *Controversy in Internal Medicine*. 1966, 96-100.

12. Relman, A.S., "Comment", in *Controversy in Internal Medicine.* 1966, 101-102.

13. Interview with Edward Freis, M.D., May 27, 1997 at Dr. Freis's office at the Washington, DC VAMC.

14. Mirsky, I.A. and Fries, E.D., "Renal and hepatic injury in trypsin "shock"." *Proc Soc Exp Biol Med,* 1944. **57**: 278.

15. Freis, E.D. and Wilkins, R.W., "The effects of pentaquine in patients with hypertension,." *Proc Soc Exp Biol Med*, 1947. **64**: 455-458.

16. Krayer, O. and Acheson, G.H., "The pharmacology of the veratrum alkaloids." *Physiol Rev*, 1946. **26**: 282-446.

17. Veterans Administration Central Office, *Future release*. 1956, Veterans Administration: Washington, DC.

18. Veterans Administration Cooperative Study on Antihypertensive Agents, "A double blind control study of antihypertensive agents." *Arch Int Med*, 1960. **106**: 133-148.

19. Veterans Administration Cooperative Study on Antihypertensive Agents, "A double blind control study of antihypertensive agents II." *Arch Int Med*, 1962. **110**: 222-229.

20. Veterans Administration Cooperative Study on Antihypertensive Agents, "A double blind control study of antihypertensive agents III. Chlorothiazide alone and in combination with other agents; Preliminary results." *Arch Int Med*, 1962. **110**: 230-236.

21. Interview with Lawrence Shaw, February 3, 1994 at Mr. Shaw's home.

22. Veterans Administration Cooperative Study on Antihypertensive Agents, "Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg." *JAMA*, 1967. **202**: 116-122.

23. Veterans Administration Cooperative Study on Antihypertensive Agents, "Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg." *JAMA*, 1970. **213**: 1143-1152.

24. Beeson, P.B. and McDermott, W., *Cecil-Loeb Textbook of Medicine*. Philadelphia, London, Toronto: W.B. Saunders Company, 1971, 1058-1059.

25. Ingelfinger, F.J., Ebert, R.V., Finland, M. and Relman, A.S., *Controversy in Internal Medicine II*. Philadelphia and London: W.B. Saunders Company, 1974

26. Moser, M., *Myths, misconception, and heroics; The story of the treatment of hypertension from the 1930s.* Le Jacq Communications, Inc., 1997

27. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Effects of treatment on morbidity in hypertension III. Influence of age, diastolic pressure, and prior cardiovascular disease; further analysis of side effects." *Circulation*, 1972. **45**: 991-1004.

28. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Multiclinic controlled trial of bethanidine and guanethidine in severe hypertension." *Circulation*, 1977. **55**: 519-524.

29. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Propranolol in mild HBP." *JAMA*, 1977. **237**: 2307-2310.

30. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Comparative effects of ticrynafen and hydrochlorothiazide in the treatment of hypertension." *New Eng J Med*, 1979. **301**: 293-297.

31. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Comparison of prazosin with hydralazine in patients receiving hydrochlorothiazide." *Circulation*, 1981. **64**: 772-779.

32. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. I. Results of short-term titration with emphasis on racial differences in response." *JAMA*, 1982. **248**: 1996-2003.

33. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Comparison of propranolol and hydrochlorothiazide for the initial treatment of hypertension. II. Results of long-term therapy." *JAMA*, 1982. **248**: 2004-2011.

34. Veterans Administration Cooperative Study Group on Antihypertensive Agents, "Low-dose captopril for the treatment of mild to moderate hypertension. I. Results of a 14-week trial." *Arch Int Med*, 1984. **144**: 1947-1953.

35. Materson, B.J., Reda, D.J., Cushman, W.C., Massie, B.M., Freis, E.D., Kochar, M.S., Hamburger, R.J., Fye, C., Lakshman, R., Gottdiener, J., Ramirez, E.A. and Henderson, W.G., "Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo." *New Eng J Med*, 1993. **328**: 914-921.

36. Materson, B.J., Reda, D.J., Cushman, W.C. and Henderson, W.G., "Results of combination anti-hypertensive therapy after failure of each of the components." *J Hum Hypertension*, 1995. **9**: 791-796.

37. Freis, E.D., "Improving treatment effectiveness in hypertension." *Arch Int Med*, 1999. **159**: 2517-2521.

38. Freis, E.D., Thomas, J.R., Fisher, S.G., Hamburger, R.J., Borreson, R.E., Mezey, K.C., Mukherji, B., Neal, W.W., Perry, H.M. and Taguchi, J.T., "Effects of reduction in drugs or dosage after long-term control of systemic hypertension." *Am J Card*, 1989. **63**: 702-708.

39. Amery, A., Birkenhager, W., Brixko, P., Bulpitt, C., Clement, D., Deruyttere, M., De Schaipdryver, A., Dollery, C., Fagard, R., Forette, F., Forte, J., Hamdy, R., Henry, J.F., Joossens, J.V., Leonetti, G., Lund-Johansen, P., O'Malley, K., Petrie, J., Strasser, T., Tuomilehto, J. and Williams, B., "Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial." *Lancet*, 1985. **1**: 1349-1354.

40. S.H.E.P. Cooperative Research Group, "Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension." *JAMA*, 1991. **265**: 3255-3264.

41. The Management Committee, Australian National Blood Pressure Study, "Treatment of mild hypertension in the elderly." *Med J Aust*, 1981. **2**: 398-402.

42. Coope, J. and Warrender, J.S., "Randomized trial of treatment of hypertension in elderly patients in primary care." *Br Med J*, 1986. **293**: 1145-1151.

43. Perry, H.M., "Hypertension research in the VA." *unpublished*, 1998.

Chapter 10. Smoking and Lung Cancer

Arguably, the American public takes for granted the health warnings that appear on tobacco products' packages and in their advertising. Smokers and non-smokers alike readily accept the notion that inhaling burning tobacco fumes is unhealthy. But the issue was not always as settled as it appears today. Scientific and legal battles about tobacco dot the landscape of both medicine and commerce over the past 50 years. Public and corporate acceptance of what many now consider to be a common-sense notion is a far cry from the days when smoking was considered a benign habit.

A vivid picture of just how far this subject has evolved requires only a glimpse of life among the troops of World War II. Smoking was so widespread in the military that small packages of cigarettes were routinely included in field rations. War-zone photos of soldiers at rest often depicted men taking smoking breaks; the Bill Maudlin cartoon characters portraying typical GIs Willie and Joe frequently uttered their war-time wisdom past lips from which a cigarette dangled. Cigarette manufacturers routinely sponsored radio broadcasts; one that aimed its entertainment specifically to the Armed Forces announced prizes for military units in the form of hundreds of cartons of cigarettes. The phrase "smoke if you got 'em" remains well-known to most Veterans. That the study of a connection between smoking and health first emerged from the then-obscure interests of a VA scientist seems more than just a coincidence.

Oscar Auerbach, M.D., was named one of VA's first Senior Medical Investigators in 1959. A staff pathologist at the Halloran VA hospital on Staten Island (N.Y.) from 1947 until 1952, when he moved to the new East Orange (N.J.) VA Hospital, Auerbach remained on the staff at East Orange until 1980, keeping an office there until his death in 1997 at age 92.

Figure 10.1. Oscar Auerbach, M.D.

Auerbach was a central player in VA tuberculosis trials (Chapter 5) and had been a pathologist at the Seaview tuberculosis hospital on Staten Island before joining VA. He published landmark reports on the pathology of unusual types of tuberculosis based on his Seaview experience. These included tuberculous empyema,[1] tracheobronchial tuberculosis,[2] tuberculosis of the pleura,

peritoneum and pericardium[3] and tuberculous meningitis.[4] After he joined VA, Auerbach studied the effects of the new antituberculosis drugs on the pathology of the disease.[5-9]

Auerbach became a central figure in American medicine for his studies of the relationship between smoking and lung cancer, demonstrated by his use of "smoking dogs." He was a participant in the first Surgeon General's report on the effects of smoking and was written up in *Life* magazine.[10]

Following are excerpts from an Oct. 30,. 1992, interview that this book's author conducted with Dr. Auerbach in his office at the East Orange VA Medical Center.[11]

> "When I was at Seaview, I published on tuberculosis. When I first went into the Veterans Administration, I published on the effects of antibiotic therapy (on tuberculosis). And one day, right here, I gave a clinico-pathological conference (CPC) on an individual who had died of lung cancer. As a TB pathologist, used to taking many sections of the tracheobronchial tree, I saw in the many sections all of the preliminary stages of the lung cancer, including carcinoma in situ and early invasion. This individual was exposed to chromate, so I thought it was all due to chromate.
>
> "I mused to the conference after my presentation that it would be interesting to see if we would find those same changes in the tracheobronchial tree that we saw here following smoking. So Charles Pfizer, for whom I had been a consultant, gave me money to pay four technicians overtime to work on that at night.
>
> "When I was through with the preliminary report, somehow or other Ed Murrow got wind of it and sent his man up and asked me if I would go on his program, *See It Now*. I felt it was too preliminary and wouldn't do it. So I presented the preliminary changes at the American College of Chest Physicians in Atlantic City somewhere around 1952 or 1953. The Cancer Society became interested in our studies, and we had a press conference, and that was the beginning of the explosion as far as I'm concerned. It was really quite something.
>
> "Everybody was interested. The American Cancer Society called a press conference, and asked me if I would appear at what was the then the Pennsylvania Hotel in New York. Around that table were all of the big reporters. They all were around the table and quizzed me. I never knew the power of the press until the next week. One of the people at the press conference was a column writer for the *New York Times*. There was a whole story on me on the op-ed page of the *New York Times*. It appeared in papers throughout the country.
>
> "I presented my material to the American Cancer Society, and from then on all our studies were done with an epidemiologist at the American Cancer Society, Cuyler Hammond.
>
> "The original results which I showed were the presence of these precancers. I drew no conclusions. These were published in (the journal) *Cancer.*[12]
>
> "As I said, we drew no conclusions. But there were sufficient changes in the tracheobronchial tree to warrant our going on with the study. I saw that we needed more material. That was a preliminary study with no conclusions drawn.

"I had been in the Navy with Charles Cameron, who was the Medical Director of the Cancer Society. Dr. Perdy Stout, who was my consultant at that time, and I went to see him. They brought in Dr. Hammond and Dr. Weaver, who was then the Research Director. And Dr. Hammond really began a dance all over the place. He said, 'What your slides are showing is what we have been saying epidemiologically, but they wouldn't listen to us.' And see, this was the proof. So he became very excited. And he said, would you let me work with you? I said that I would let him work with me on one condition, that he become a co-author. He said, 'That's very generous. You know, I've been asked by the Cancer Society to help you.' We made quite a team. So you notice that his name is on all the papers.

"The Cancer Society people were very excited. They said that they would support us. And for all the years after that, we were supported by the American Cancer Society.

"It was very, very, very interesting. I would go into the American Cancer Society, and I would sit down with Cuyler Hammond and with Lawrence Garfinkel, who took his place. E. Cuyler Hammond was the world's best and best-known epidemiologist in the field of smoking. No question about it. This all happened in the early 50s.

(Meanwhile, what were you doing at VA?)

"I was a routine pathologist, carrying on with all my work. I did the research at home at night and on weekends. For years I did that.. . It was all day Sunday. And I'd start about 4 in the morning and work until about 6:30. I would go home after work and sometimes work until 10:00 at night. And all day Saturday, all day Sunday. It was something I loved. I enjoyed doing it....

"Well, here's what would happen. I would go and see Cuyler Hammond at the American Cancer Society and we sat and we talked. And he said, 'Oscar, what are you trying to do?' I said, 'Simple. I am trying to see, in individuals who die of lung cancer, whether they show all the changes preliminary to the development of invasive carcinoma.[13] If I prove that, am I also able to see those same changes in individuals who die of causes other than lung cancer? And are they proportional to the amount of cigarettes they smoke?'[14]

"And those were the two studies all the way through, except one, which came later: What happens when individuals give up the smoking habit? That became the article that was published in the *New England Journal of Medicine*[15, 16] on former cigarette smokers."

The first, 1964 Surgeon General's report on *Smoking and Health* includes a section on these anatomical studies.[17] That report reviewed the results of attempts up to that time to induce lung cancer in experimental animals from smoking. They concluded that all studies up to that time were inconclusive.[18]

(When did you decide to set up your experimental dog model?)

"I'll tell you what happened. There was an advertisement by one of the tobacco companies. A

full-page ad, which said that it is interesting that no animal model was used. That inspired me. And so I did one study on animals. They were all thoroughbred beagles. I did it with Cuyler. Ten smoking dogs versus 10 non-smoking dogs.

(How did you get the dogs to smoke?)

"Tracheostomy. That study set the pace. It was at that time that we saw that we could produce the same changes in the tracheobronchial tree as we saw in human beings right up to invasion. And that was published.[19] Then we were beset by the tobacco industry. But that never bothered me and the tobacco industry never bothered me.

(What did they do?)

"Oh, the tobacco industry would always write articles. When I went to have articles published in the *Archives of Environmental Health*, they threatened the editor. They also went to the AMA and tried to have my article withdrawn.

(What kind of pressure could they use?)

"Oh, they would take their advertisements out of the papers. I had a story in *Life* magazine. A very pretty young woman was doing the story for them. And the tobacco industry threatened *Life* magazine, that if they wrote that story, they were going to withdraw their ads. She told me that the editorial board, all the editorial board, had a meeting and stated that they were completely behind the story that she wrote. And the article was published....

"When we were studying the smoking dogs, they got the antivivisectionists after us.

(How did you decide to use dogs first of all?)

"I sat down with Cuyler Hammond and Arthur Purdy Stout. I said that, if we were going to do an animal model, the tracheobronchial tree must be large enough so that we could examine it. It must be one in which we could see the same changes as in the human being if they really occur. Dr. Hammond said that we want no variables. He insisted upon one breed and one sex, males.

"We found that using a tracheostomy was the best way to teach the dogs how to inhale. We later found out that they inhale by themselves after a while. But with the tracheostomy, we had complete control of how much smoke would go in . . . What happened (in the preliminary study) was that one died after 29 days. Another dog died after 200-some-odd days, another after 410 days, another after 415, and another after 420. We found that they were developing pulmonary infarcts. I called Cuyler Hammond, and said we'd better end this trial now while we still have good tracheobronchial trees to examine. So five dogs were sacrificed from 420 to 423 days. And we found that they developed pulmonary embolisms from thrombi that would develop in the right atrial appendage. The control dogs didn't have any changes.[19]

"We did the larynx. We did the esophagus. We did the lung parenchyma. Our studies on

> emphysema were equally as important as our studies on the tracheobronchial tree. All related to the smoking effects. Every study in the dog paralleled that of the human being.
>
> "And always, I want you to know, we were pursued by the tobacco industry, but that was nothing. That didn't bother me. Never. They got hold of the Congressmen and Senators..... They wrote to Dr. Middleton and Dr. Middleton called me and said, 'Oscar, I want you to know they asked why the Veterans Administration was supporting a doctor who was killing an important industry in the southern states?' And his answer was, 'I never interfere in the scientific pursuits of the people who are under me.' I received the same support from Ben Wells, Jim Musser and Hal Engle. Bill Middleton knew everything I was doing. So did Jim Musser and Ben Wells."

Auerbach's definitive study of smoking dogs involved a total of 97 male beagles, eight nonsmoking controls with tracheostomies in place and the rest smoking various numbers of cigarettes, both filter-tipped and unfiltered. After almost three years, all the nonsmoking dogs had normal lungs. Histopathological changes had occurred in the lungs of all the smoking dogs, with the greatest changes in the lungs of dogs smoking unfiltered cigarettes most heavily.[20] Ten of the 24 dogs in the latter group developed invasive bronchiolo-alveolar tumors.[21] They also showed pulmonary fibrosis with emphysema.[22, 23] In another study, Auerbach demonstrated thickening of the arteriolar walls in the myocardia of smoking dogs and humans.[24]

Auerbach later studied other environmental effects on lung cancer. He collaborated with Geno Saccomanno, M.D., Ph.D., of the Grand Junction (Colo.) VA Hospital, who studied the factors leading to lung pathology among the uranium miners of the Colorado plateau.[25-32] He collaborated on studies of arsenic[33] and asbestos[34, 35] exposure and of inhalants[36] to lung cancer.

Auerbach's landmark contributions were the result of intense and laborious observation. His laboratory was lined floor to ceiling with slides. A typical study involved 208 serial section slides on each of 117 cases, each containing more than 24,000 slides and each studied, in most cases, by Auerbach himself. He also had expert statistical collaboration from his first studies on the lung cancer problem, and randomization and "blinding" were the rule. Auerbach's work has made a lasting impact on the health of millions.

References

1. Auerbach, O., "Empyema as a complication of chronic pulmonary tuberculosis." *Am Rev Tuberc*, 1949. **59**: 601-618.

2. Auerbach, O., "Tuberculosis of the trachea and major bronchi." *Am Rev Tuberc*, 1949. **60**: 604-620.

3. Auerbach, O., "Pleural, peritoneal and pericardial tuberculosis - a review of 209 cases uncomplicated by treatment or secondary infection." *Am Rev Tuberc*, 1950. **61**: 845-861.

4. Auerbach, O., "Tuberculous meningitis: Correlation of therapeutic results with the pathogenesis and pathologic changes." *Am Rev Tuberc*, 1951. **64**: 408-429.

5. Auerbach, O., Weiss, L. and Stemmerman, G., "Pathology of tuberculosis treated with streptomycin: A review of 34 cases." *Dis Chest*, 1951. **19**: 145-157.

6. Auerbach, O., Katz, H.I. and Small, M., "The effect of streptomycin therapy on the bronchocavitary junction and its relation to cavity healing." *Am Rev Tuberc*, 1953. **67**: 173-200.

7. Auerbach, O., Hobby, G., Small, M., Lenert, T. and Vaughn, L., "Effect of degree of healing upon persistence of tubercle bacilli within pulmonary lesions." *Am Rev Tuberc*, 1955. **72**: 386-389.

8. Auerbach, O., "Pulmonary tuberculosis after the prolonged use of chemotherapy." *Am Rev Tuberc*, 1955. **71**: 165-185.

9. Auerbach, O., Hobby, G., Small, M., Lenert, T. and Comer, J., "The clinicopathologic significance of the demonstration of viable tubercle bacilli in resected lesions." *J Thorac Surg*, 1955. **29**: 109-132.

10. "New cigarette-cancer link." *Life Magazine*, June 11, 1956, Cover and pp 129-130.

11. Interview with Oscar Auerbach, M.D., October 30, 1992 at Dr. Auerbach's office at the East Orange, NJ, VA Medical Center.

12. Auerbach, O., Petrick, T.G., Stout, A.P., Statsinger, A.L., Muehsam, G.E., Forman, J.B. and Gere, J.B., "The anatomical approach to the study of smoking and bronchogenic carcinoma." *Cancer*, 1956. **9**: 76-83.

13. Auerbach, O. and Stout, A.P., "Histopathological aspects of occult cancer of the lung." *Ann N Y Acad Sci*, 1964. **114**: 803-810.

14. Auerbach, O., Stout, A.P., Hammond, E.C. and Garfinkel, L., "Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer." *N Engl J Med*, 1961. **265**: 253-267.

15. Auerbach, O., Stout, A.P., Hammond, E.C. and Garfinkel, L., "Bronchial epithelium in former smokers." *N Engl J Med*, 1962. **267**: 119-125.

16. Auerbach, O., Stout, A.P., Hammond, E.C. and Garfinkel, L., "Smoking habits and age in relation to pulmonary changes: Rupture of alveolar septums, fibrosis and thickening of walls of small arteries and arterioles." *N Engl J Med*, 1963. **269**: 1045-1054.

17. Surgeon General of the United States *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. U.S. Department of Health, Education and Welfare; Public Health Service, 1964. 167-173.

18. Surgeon General *Smoking and Health*. 1964. 165.

19. Auerbach, O., Hammond, E.C., Kirman, D., Garfinkel, L. and Stout, A.P., "Histologic changes in bronchial tubes of cigarette-smoking dogs." *Cancer*, 1967. **20**: 2055-2066.

20. Hammond, E.C., Auerbach, O., Kirman, D. and Garfinkel, L., "Effects of cigarette smoking on dogs: 1. Design of experiment, mortality, and findings in lung parenchyma." *Arch Environ Health*, 1970. **21**: 740-753.

21. Auerbach, O., Hammond, E.C., Kirman, D. and Garfinkel, L., "Effects of cigarette smoking on dogs. II. Pulmonary neoplasms." *Arch Environ Health*, 1970. **21**: 754-768.

22. Frasca, J.M., Auerbach, O., Parks, V.R. and Jamieson, J.D., "Electron microscopic observations on pulmonary fibrosis and emphysema in smoking dogs." *Exp Mol Pathol*, 1971. **15**: 108-125.

23. Frasca, J.M., Auerbach, O., Parks, V.R. and Jamieson, J.D., "Alveolar cell hyperplasia in the lungs of smoking dogs." *Exp Mol Pathol*, 1974. **21**: 300-312.

24. Auerbach, O., Hammond, E.C., Garfinkel, L. and Kirman, D., "Thickness of walls of myocardial arterioles in relation to smoking and age. Findings in men and dogs." *Arch Environ Health*, 1971. **22**: 20-27.

25. Saccomanno, G., Archer, V.E., Saunders, R.P., James, L. and Beckler, P.A., "Lung cancer of uranium workers on the Colorado Plateau." *Health Physics*, 1964. **10**: 1195-1201.

26. Saccomanno, G., Archer, V.E., Auerbach, O., Kuschner, M., Saunders, R.P. and Klein, M.G., "Histologic types of lung cancer among uranium miners." *Cancer*, 1971. **27**: 515-523.

27. Saccomanno, G., Archer, V.E., Auerbach, O. and Saunders, R.P., "Susceptibility and resistance to environmental carcinogens in the development of carcinoma of the lung." *Hum Pathol*, 1973. **4**: 487-495.

28. Saccomanno, G., Archer, V.E., Saunders, R.P., Auerbach, O. and Klein, M.G., "Early indices of cancer risk among uranium miners with reference to modifying factors." *Ann N Y Acad Sci*, 1976. **271**: 377-383.

29. Auerbach, O., Saccomanno, G., Kuschner, M., Brown, R.D. and Garfinkel, L., "Histologic findings in the tracheobronchial tree of uranium miners and non-miners with lung cancer." *Cancer*, 1978. **42**: 483-489.

30. Saccomanno, G., Yale, C., Dixon, W., Auerbach, O. and Huth, G.C., "An epidemiological analysis of the relationship between exposure to Rn progeny, smoking and bronchogenic carcinoma in the U-mining population of the Colorado Plateau--1960-1980." *Health Phys*, 1986. **50**: 605-618.

31. Saccomanno, G., Huth, G.C., Auerbach, O. and Kuschner, M., "Relationship of radioactive radon daughters and cigarette smoking in the genesis of lung cancer in uranium miners." *Cancer*, 1988. **62**: 1402-1408.

32. Saccomanno, G., Auerbach, O., Kuschner, M., Harley, N.H., Michels, R.Y., Anderson, M.W. and Bechtel, J.J., "A comparison between the localization of lung tumors in uranium miners and in nonminers from 1947 to 1991." *Cancer*, 1996. **77**: 1278-1283.

33. Wicks, M.J., Archer, V.E., Auerbach, O. and Kuschner, M., "Arsenic exposure in a copper smelter as related to histological type of lung cancer." *Am J Ind Med*, 1981. **2**: 25-31.

34. Auerbach, O., Hammond, E.C., Selikoff, I.J., Parks, V.R., Kaslow, H.D. and Garfinkel, L., "Asbestos bodies in lung parenchyma in relation to ingestion and inhalation of mineral fibers." *Environ Res*, 1977. **14**: 286-304.

35. Auerbach, O., Garfinkel, L., Parks, V.R., Conston, A.S., Galdi, V.A. and Joubert, L., "Histologic type of lung cancer and asbestos exposure." *Cancer*, 1984. **54**: 3017-3021.

36. Weiss, W., Moser, R.L. and Auerbach, O., "Lung cancer in chloromethyl ether workers." *Am Rev Respir Dis*, 1979. **120**: 1031-1037.

Chapter 11. Radioimmunoassay—A Revolutionary Advance in Medicine

If there has ever been any skepticism about the quality of medical research being done within the VA health care system, such doubts were forever dispelled with a signal event in 1977. A dedicated and relentless VA physicist and a VA scientist studying hormones each gained the world's attention by being awarded the Nobel Prize in Physiology or Medicine. Rosalyn Yalow, Ph.D., of the Bronx VA Medical Center captured science's crown jewel for her groundbreaking work in the field of radioimmunoassay (RIA), a process by which substances in the blood can be measured with exquisite accuracy. Andrew F. Schally, Ph.D., earned the recognition for his research at the New Orleans VA Medical Center on hormone activity in the hypothalamus gland.

The breakthrough work by Yalow and her colleague Solomon Berson, M.D., was supported from its inception by the Radioisotope Service at the Bronx VA Hospital. The RIA achievement is a testimony to the skill of Drs. Yalow and Berson and to the value of VA's policy of providing sustained support to talented and productive medical researchers.

RIA works by combining an unknown amount of the substance to be measured with an antibody that will bind to it in a reversible way, so that after a time the bound and unbound amounts of the substance will reach equilibrium. It is also mixed with a radioactive version of the material to be measured. Since the binding of the radioactive form competes with the stable form for binding on the antibody, the known radioactive form can be used as a "tracer" for the behavior of the unknown amount of the stable form and will achieve the same bound-to-unbound equilibrium as does the substance to be measured. When the amount of antibody present is enough to bind only part of the material to be measured, it will also bind only that same fraction of the radioactive tracer. The more substance to be measured, the more will be left after saturating the antibody binding. Since this is equally true for the tracer, one can measure the percent of bound tracer and thus accurately measure the unknown. The Nobel Prize announcement provided this example:

> "The percentage binding of labeled insulin to the antibodies is a function of the total insulin concentration in the solution… RIA is so sensitive that it allowed determination of insulin in amounts as small as 10-20 pg and ACTH in an amount less that 1 pg (or one thousand-billionth g) per ml."[1]

The discovery of RIA dates back some 30 years before it culminated with the Nobel award. In late 1947, Bernard Roswit, M.D., set up a Radioisotope Unit at the Bronx VA Hospital, one of the original seven units approved by Herbert Allen, M.D.[2] (Chapter 6). Roswit's first hire, in December 1947, was the young physicist Rosalyn Yalow[3] who wanted to work with radioisotopes. Yalow's training was in nuclear physics, with a Ph.D. degree earned in 1945 at the University of Illinois. Her first job was working as an electrical engineer for International Telephone and Telegraph, a leading worldwide telecommunications company. Yalow next moved to teaching, joining the physics faculty at Hunter College in the Bronx.

Yalow very much wanted to pursue her interest in research even though Hunter possessed no such facilities. Her training in nuclear physics had fostered an interest in radioisotopes and a curiosity

that was stimulated by her husband's use of radioiodine in the treatment of patients with thyroid disease. She visited Dr. Edith H. Quimby, Sc.D. at Montefiore Hospital in New York, who agreed to teach her about radioisotopes and introduced her to Gioacchino (Gino) Failla, Sc.D.. In addition to their research activities at Montefiore, Quimby and Fialla were radiology consultants at the Bronx VA Hospital. Through them, Yalow met Bernard Roswit, M.D., Chief of Radiation Therapy at VA.

At first, Yalow performed her VA work while "moonlighting" from her teaching job, but in 1949 she opened her own VA-based laboratory. Early papers were eclectic and reflected the interests of her clinician colleagues. With Roswit, she studied radioactive phosphorus (^{32}P) in diagnosis of testicular cancer[4] and radioactive iodine (^{131}I) in treatment of metastatic thyroid cancer.[5] With others, she studied dosimetry in diagnostic radiology,[6] variability of bone marrow biopsies,[7] and the clearance of radiosodium from skin and muscle.[8-11]

Figure 11.1. Rosalyn Yalow, Ph.D., in her laboratory

In 1950, an opportunity arose to recruit a physician colleague for the Radioisotope Unit. Yalow recalled:

> "It seemed to me... that the future of radioisotopes in medicine was not in radiotherapy, in spite of the 'atomic cocktail'... but that the way to go would be physiology—that we needed somebody trained in internal medicine. So I went to the Head of Medicine at the hospital here, Dr. Bernard Straus, and said, 'We'll take anybody you recommend.'
>
> "And he said, 'I have a brilliant resident. He's already accepted the position at another VA Hospital but I'll send him down to you.' And so Sol came down, and we interacted very well, and he gave up the other job."

Solomon Berson, M.D., was just finishing his internal medicine residency in the Mt. Sinai-Bronx VA-affiliated program. He had already shown a talent for clinical research and was an author on papers about Hodgkin's Disease[12, 13] and rheumatoid arthritis.[14] For the first year or so after he joined VA, he worked there only part-time and also carried on a private practice. Soon, he gave up

his practice and worked full time at VA, because he found the work so exciting. In 1954, when the radioisotope unit was separated from Radiotherapy and became a separate Radioisotope Service at the hospital, Berson became its Chief.

Figure 11.2. Solomon Berson, M.D.

The first collaborative work by Berson and Yalow were studies of ^{32}P and ^{42}K labeled red blood cells for studies of blood volume and red-cell disorders.[15-17]

Soon they began to study the thyroid. Yalow developed an improved Geiger counter for detection of the ^{131}I gamma ray. They worked out a method for measuring iodine clearance by the thyroid gland and applied it to a variety of clinical conditions. In 1954, they published what was probably the first comprehensive model of thyroid iodine metabolism.[18-20]

Next their attention was directed to ^{131}I labeled human serum albumin, and they began studying albumin metabolism and blood volume in humans, both well and ill.[21-26] Two early research fellows in the lab, Marcus Rothschild, M.D., and Arthur Baumann, M.D.,[27] worked on the albumin studies, which Rothschild later extended to important work on albumin production by the liver.

Rothschild and Baumann also collaborated on the laboratory's first studies of metabolism of insulin, which Yalow labeled with ^{131}I. These studies were stimulated by Arthur Mirsky's theory that adult-onset (Type 2) diabetes was caused by an excessive rate of metabolism of insulin, as it was known that the pancreas of these patients contained insulin. Mirsky's theory would predict that insulin would disappear faster from the blood of diabetic patients than from the blood of normal subjects. Instead, the opposite occurred.

Yalow described how the process worked:

> "We labeled the insulin with (radio) iodine, gave it intravenously, and noted that there was a slower disappearance in the adult diabetics, rather than faster, which the theory had predicted. Although there was an occasional patient who was a 'rapid disappearer' when his diabetes was first discovered, he then converted to a 'slow disappearer' after three months of insulin therapy. And then we had schizophrenic patients who had had insulin shock therapy who were also 'slow disappearers'. So we thought this was due to the development of antibody."

But the notion of an antibody to insulin was too iconoclastic for the medical establishment, and this led to difficulty in publication[28] of this pivotal discovery, the basis for the concept of radioimmunoassay:

> "We were able to demonstrate that, yes, in the plasma of insulin-treated patients, the labeled insulin was bound to something that had the characteristics of a gamma globulin. We submitted the paper to *Science*; they rejected it. We submitted the paper to the *Journal of Clinical Investigation*; they rejected it... We reached a compromise with the (*JCI*) editor. Instead of calling it an antibody we called it a binding globulin, because they agreed that we had demonstrated it had the characteristics of a gamma globulin. But in those days *everybody* knew peptides smaller than 10,000 were not antigenic. Therefore, insulin could not be antigenic. Therefore we couldn't call it an antibody."

So the key publication reporting the binding of insulin to an antibody[28] used the term "binding globulin," but, within a year or so, the presence of insulin antibodies was well accepted.

Over the next three years, Berson and Yalow published elegant characterizations of these antibodies.[29-35] As they assayed the antibodies using various amounts of insulin, they realized that they could turn the process around. A fixed amount of antibody would bind a certain amount of insulin. If the balance between antibody and insulin were optimal, the fraction of the insulin (or radioactive insulin) that bound to the antibody would relate to the total amount of insulin present.

While this concept is as simple as it is elegant, carrying it forward to a usable assay required intense work and thought. The antibody had to be just right. The balance in the assay had to be correct. At first, they succeeded in measuring insulin added to human blood, but the assay was not sensitive enough to measure the insulin in normal serum. They were very careful, checking and cross-checking. Eventually, they were confident they could measure insulin in normal human serum. A preliminary report showing insulin response to glucose in two human subjects appeared in *Nature* in 1959.[36] The definitive report presenting the radioimmunoassay of human insulin, including glucose response studies in 96 patients, appeared in the *Journal of Clinical Investigation* in 1960.[37]

Successful radioimmunoassay of insulin led to an explosion of assays. As Berson and Yalow continued refining their method, others were trying to apply the same concept to other hormones. The Radioisotope Service at the Bronx VA Hospital played an active role. Even before the 1960 paper was published, Berson and Yalow helped Dr. Roger Unger, who used the same concept to measure circulating glucagon in human subjects, to get started (Chapter 7). Now many others sought their instruction. Yalow saw the two journal articles as the sparks that ignited more widespread interest in the field. She noted::

"[O]ver the next four or five years, we gave four training programs in which, at no charge, we invited endocrinologists—anybody who wanted to come. And I think we trained 140 people. And... those people started to produce an awful lot of papers, and that's how immunoassay took off."[3]

In 1963, Seymour Glick, M.D., and Jesse Roth, M.D., both fellows in the Berson-Yalow laboratory, published with Yalow and Berson a successful method to assay human growth hormone in normal human plasma.[38] In 1963, Berson and Yalow, with Gerald Aurbach, M.D. and John Potts, M.D. of

the NIH, published a report on radioimmunoassay of parathyroid hormone,[39] though this assay still required a lot of work before it could be used routinely.

The following year Berson and Yalow published a preliminary report with Drs. Glick and Roth on the assay of ACTH extracted from plasma.[40] This was followed by years of painstaking development to increase the sensitivity of the assay, necessary since ACTH is present in very small concentrations in normal human plasma. Eventually, in 1968, they published a method for radioimmunoassay of ACTH in unextracted plasma, together with its application in a variety of physiological and clinical states.[41]

Figure 11.3. Yalow and one of the guinea pigs whose antibodies made radioimmunoassay possible

Paralleling the development of assays and improvements in techniques, there was constant study of patients and physiological processes. As Yalow said, "We never developed assays to develop assays. We developed assays to deal with physiologic problems."[3] The insulin assay led to studies of insulin metabolism in normal people and diabetic patients.[42-45] Development of the human growth hormone assay was followed by studies of the physiology of growth hormone, made possible by this new tool. Most important was their demonstration that hypoglycemia caused a marked rise in growth hormone levels.[46, 47] In 1969 the group showed that different types of stress had different effects on ACTH and growth hormone response.[48]

In 1968, Solomon Berson left VA to become the founding Chair of the Department of Medicine at the new Mount Sinai School of Medicine. However, he did not move his research to Mount Sinai, and Yalow remained at the Bronx VA Hospital, now as Chief, Radioisotope Service. From that time until his sudden death in 1972, Berson continued to work at VA laboratory when he could, generally late at night, but Yalow managed the day-to-day operation of the research.

The laboratory entered a new field, gastrointestinal hormones, which Yalow and her colleagues studied over several years. The first of the hormones they looked at was gastrin. At the same time,

they produced an assay for the Australia antigen, the virus that causes hepatitis B. This assay made it possible for blood banks everywhere to detect the hepatitis B-causing virus in blood donations, to prevent the transmission of this virulent disease.

Figure 11.4. Rosalyn Yalow, Roger Unger, Solomon Berson and Erik Jorpes at the Nobel Conference on Gastrointestinal Hormones in 1970

Yalow described how the hepatitis B assay came about:

> "When we described the gastrin assay, Mort Grossman was expecting John Walsh, who had been at the NIH, to come to him in the Career Development Program. And so he felt it would be a good idea if John Walsh came here to learn the gastrin assay before he went out to Mort Grossman. And I was in Washington, so I thought I ought to take John out to lunch and, you know, get to know him a bit."

Walsh was studying the Australia antigen, the marker for infectious hepatitis B, and Yalow expressed an interest in working together to develop an assay to detect it. She said:

> "We used ourselves and our technicians as our controls. And so I labeled the Australia antigen, and purified it on the G200 column, and then we added it to control plasma, and its behavior in my plasma was different from its behavior in the plasma of two of the technicians here. And it turned out that those two technicians had been sent to the South Pacific, during the War. They had the yellow fever vaccine which was contaminated with the virus. They had antibody. So we had an assay going, immediately. We didn't have to immunize a guinea pig."[3]

After Berson's death in 1972, Yalow continued to extend the radioimmunoassay to new uses. The laboratory was named the "Solomon A. Berson Research Laboratory," and a fellowship in Berson's

name was established to support young researchers in the laboratory.

Yalow and Berson had been nominated for the Nobel Prize while Berson was still alive. Now that he had died and was not eligible for the prize, her work alone would have to earn the recognition. Over the next years, she and her young colleagues developed a major body of work on hormones and prohormones,[49-59] on the many locations of hormones previously associated with a single site,[60-62] and on hormones in malignancies.[63, 64] She and Ludwig Gross, M.D., developed a radioimmunoassay for the mouse leukemia virus that Gross had discovered.[65] Yalow continued to make contributions, all from a modest laboratory in which she herself could vouch for every finding.

Throughout Yalow's research career, VA consistently supported her research. She asserted that she had never applied for a grant from the NIH or other agencies. She in turn was most loyal to the institution that had nourished her career. In all her contacts, she proudly acknowledged VA as her home base and the source of support for her research.

Finally, in 1977, Rosalyn Yalow received the Nobel Prize for the development of radioimmunoassays of peptide hormones. She was the second woman to receive the award in the category of "Physiology or Medicine."

Figure 11.5. Rosalyn Yalow receiving the Nobel Prize

The magnitude of her work was captured in the formal Nobel announcement:

> "RIA brought about a revolution in biological and medical research. We have today at our disposal a large number of RIA-like procedures, so-called ligand methods, for determination of almost anything we wish to measure: peptide hormones, hormones that are not peptides, peptides that are not hormones, enzymes, viruses, antibodies, drugs of the most different kinds, etc. This has brought about an enormous development in hitherto closed areas of research.
>
> "Yalow's contributions were not limited to presenting us with RIA. In a series of classical articles she and her coworkers, with the aid of RIA, were able to elucidate the physiology of the peptide hormones insulin, ACTH, growth hormone, and also to throw light upon the pathogenesis of diseases caused by abnormal secretion of these hormones. Thus, they directed diabetes research into new tracks and gave it a new dimension. This was pioneering work at the highest level. It had an enormous impact. We were witnessing the birth of a new era in endocrinology, one that started with Yalow."[1]

The young physicist from a modest family, who as a student had been urged to use stenography as a back door into science, had found in VA her opportunity to thrive and to make an important contribution.[66]

References

1. Karolinska Institutet, *The 1977 Nobel Prize in Physiology or Medicine*. 1977: Stockholm, Sweden.

2. Lyon, G., *Summary of Radioisotope Labs (Handwritten Notes)*. 1957.

3. Interview with Rosalyn Yalow, Ph.D., October 28, 1992 at her office at the Bronx VA Medical Center.

4. Roswit, B., Sorrentino, J. and Yalow, R., "Use of radioactive phosphorus (P32) in diagnosis of testicular tumors; Preliminary report." *J Urol*, 1950. **63**: 724-728.

5. Sorrentino, J., Roswit, B. and Yalow, R., "Thyroid carcinoma with multiple metastases and pathologic fracture, successfully treated with radioiodine; Report of a case." *Radiology*, 1951. **57**: 729-737.

6. Sorrentino, J. and Yalow, R., "Nomogram for dose determinations in diagnostic radiology." *Radiology*, 1950. **55**: 748-753.

7. Fadem, R.S. and Yalow, R., "Uniformity of cell counts in smears of bone marrow particles." *Am J Clin Path*, 1951. **21**: 541-545.

8. Conway, H., Roswit, B., Stark, R.B. and Yalow, R., "Radioactive sodium clearance as test of circulatory efficiency of tubed pedicles and flaps." *Proc Soc Exp Biol Med*, 1951. **77**: 348-351.

9. Wisham, L.H., Yalow, R. and Freund, A.J., "Consistency of clearance of radioactive sodium from human muscle." *Am Heart J*, 1951. **41**: 810-818.

10. Wisham, L.H. and Yalow, R., "Some factors affecting clearance of Na24 from human muscle." *Am Heart J*, 1952. **43**: 67-76.

11. Freund, J., Wisham, L.H. and Yalow, R.S., "Effect of priscoline on clearance of radiosodium from muscle and skin of man in normal and diseased limbs." *Circulation*, 1953. **8**: 89-97.

12. Straus, B., Berson, S.A., Bernstein, T.C. and Jacobson, A.S., "Guanazolo in therapy of Hodgkin's disease." *Blood*, 1950. **5**: 1059-1061.

13. Fadem, R.S., Berson, S.A., Jacobson, A.S. and Straus, B., "Effects of cortisone on bone marrow in Hodgkin's disease." *Am J Clin Path*, 1951. **21**: 799-813.

14. Guest, C.M., Kammerer, W.H., Cecil, R.L. and Berson, S.A., "Epinephrine, pregnenolone and testosterone in treatment of rheumatoid arthritis." *JAMA*, 1950. **143**: 338-344.

15. Yalow, R. and Berson, S.A., "Use of K42 tagged erythrocytes in blood volume determinations." *Science*, 1951. **114**: 14-15.

16. Berson, S.A. and Yalow, R., "Use of K42 or P32 labelled erythrocytes and I131 tagged human serum albumin in simultaneous blood volume determinations." *J Clin Invest*, 1952. **31**: 572-580.

17. Berson, S.A., Yalow, R.S., Azulay, A., Schreiber, S.S. and Roswit, B., "The biologic decay curve of P32 tagged erythrocytes. Application to study of acute changes in blood volume." *J Clin Invest*, 1952. **31**: 581-591.

18. Berson, S.A. and Yalow, R.S., "The effect of cortisone on the iodine accumulating function of the thyroid gland in euthyroid subjects." *J Clin Endocrinol Metab*, 1952. **12**: 407-422.

19. Berson, S.A., Yalow, R.S., Sorrentino, J. and Roswit, B., "The determination of thyroidal and renal plasma I131 clearance rates as a routine diagnostic test of thyroid dysfunction." *J Clin Invest*, 1952. **31**: 141-158.

20. Berson, S.A. and Yalow, R.S., "Quantitative aspects of iodine metabolism. Exchangeable organic iodine pool, and rates of thyroidal secretion, peripheral degradation and fecal excretion of endogonously synthesized organically bound iodine." *J Clin Invest*, 1954. **33**: 1533-1552.

21. Berson, S.A. and Yalow, R.S., "Distribution of I131 labelled human serum albumin introduced into ascitic fluid: Analysis of kinetics of 3 compartment catenary transfer system in man and speculations on possible sites of degradation." *J Clin Invest*, 1954. **33**: 377-387.

22. Rothschild, M.A., Bauman, A., Yalow, R.S. and Berson, S.A., "Effect of splenomegaly on blood volume." *J Appl Physiol*, 1954. **6**: 701-706.

23. Schreiber, S.S., Bauman, A., Yalow, R. and Berson, S.A., "Blood volume alterations in congestive heart failure." *J Clin Invest*, 1954. **33**: 578-586.

24. Vazquez, O.N., Newerly, K., Yalow, R. and Berson, S.A., "Estimation of trapped plasma with I131 albumin; Critique of methods." *J Appl Physiol*, 1954. **6**: 437-440.

25. Bauman, A., Rothschild, M.A., Yalow, R. and Berson, S.A., "Distribution and metabolism of I131 labeled human serum albumin in congestive heart failure with and without proteinurea." *J Clin Invest*, 1955. **34**: 1359-1368.

26. Rothschild, M.A., Bauman, A., Yalow, R. and Berson, S.A., "Tissue distribution of I131 labelled human serum albumin following intravenous administration." *J Clin Invest*, 1955. **34**: 1354-1358.

27. Interview with Marcus A. Rothschild, M.D., February 8, 1994 at Dr. Rothschild's home in Florida.

28. Berson, S.A., Yalow, R., Bauman, A., Rothschild, M.A. and Newerly, K., "Insulin-I131 metabolism in human subjects: Demonstration of insulin binding globulin in the circulation of insulin-treated subjects." *J Clin Invest*, 1956. **35**: 170-190.

29. Berson, S.A. and Yalow, R.S., "Ethanol fractionation of plasma and electrophoretic identification of insulin-binding antibody." *J Clin Invest*, 1957. **36**: 642-647.

30. Berson, S.A. and Yalow, R.S., "Studies with insulin-binding antibody." *Diabetes*, 1957. **6**: 402-405.

31. Berson, S.A. and Yalow, R.S., "Insulin antagonists, insulin antibodies and insulin resistance." *Am J Med*, 1958. **25**: 13S-18S.

32. Berson, S.A. and Yalow, R.S., "Species-specificity of human antibeef, pork insulin serum." *J Clin Invest*, 1959. **38**: 2017-2025.

33. Berson, S.A. and Yalow, R.S., "Recent studies on insulin-binding antibodies." *Ann NY Acad Sci*, 1959. **82**: 338-344.

34. Berson, S.A. and Yalow, R.S., "Quantitative aspects of the reaction between insulin and insulin-binding antibody." *J Clin Invest*, 1959. **38**: 1996-2016.

35. Berson, S.A. and Yalow, R.S., "Cross reactions of human anti-beef, pork insulin with beef, pork, sheep, horse and human insulins." *Fed Proc*, 1959. **18**: 11.

36. Yalow, R.S. and Berson, S.A., "Assay of plasma insulin in human subjects by immunological methods." *Nature*, 1959. **184 (Suppl 21)**: 1648-1649.

37. Yalow, R.S. and Berson, S.A., "Immunoassay of endogenous plasma insulin in man." *J Clin Invest*, 1960. **39**: 1157-1175.

38. Glick, S.M., Roth, J., Yalow, R.S. and Berson, S.A., "Immunoassay of human growth hormone in plasma." *Nature*, 1963. **199**: 784-787.

39. Berson, S.A., Yalow, R.S., Aurbach, G.D. and Potts, J.T., "Immunoassay of bovine and human parathyroid hormone." *Proc Natl Acad Sci USA*, 1963. **49**: 613-617.

40. Yalow, R.S., Glick, S.M., Roth, J. and Berson, S.A., "Radioimmunoassay of human plasma ACTH." *J Clin Endocrinol Metab*, 1964. **24**: 1219-1225.

41. Berson, S.A. and Yalow, R.S., "Radioimmunoassay of ACTH in plasma." *J Clin Invest*, 1968. **47**: 2725-2751.

42. Yalow, R.S. and Berson, S.A., "Plasma insulin concentrations in nondiabetic and early diabetic subjects. Determinations by a new sensitive immuno-assay technic." *Diabetes*, 1960. **9**: 254-260.

43. Yalow, R.S. and Berson, S.A., "Comparison of plasma insulin levels following administration of tolbutamide and glucose." *Diabetes*, 1960. **9**: 356-362.

44. Berson, S.A. and Yalow, R.S., "Plasma insulin in health and disease." *Amer J Med*, 1961. **31**: 874-881.

45. Berson, S.A. and Yalow, R.S., "Insulin antibodies and insulin resistance." *Diabetes Dig*, 1962. **1**: 4.

46. Roth, J., Glick, S.M., Yalow, R.S. and Berson, S.A., "Secretion of human growth hormone: Physiologic and experimental modification." *Metabolism*, 1963. **12**: 577-579.

47. Roth, J., Glick, S.M., Yalow, R.S. and Berson, S.A., "Hypoglycemia: A potent stimulus to secretion of growth hormone." *Science*, 1963. **140**: 987-988.

48. Yalow, R.S., Varsano-Aharon, N., Echemendia, E. and Berson, S.A., "HGH and ACTH secretory responses to stress." *Horm Metab Res*, 1969. **1**: 3-8.

49. Silverman, R. and Yalow, R.S., "Heterogeneity of parathyroid hormone. Clinical and physiologic implications." *J Clin Invest*, 1973. **52**: 1958-1971.

50. Yalow, R.S. and Wu, N., "Additional studies on the nature of big big gastrin." *Gastroenterology*, 1973. **65**: 19-27.

51. Yalow, R.S., "Radioimmunoassay methodology: Application to problems of heterogeneity of peptide hormones." *Pharmacol Rev*, 1973. **25**: 161-178.

52. Coslovsky, R. and Yalow, R.S., "Influence of the hormonal forms of ACTH on the pattern of corticosteroid secretion." *Biochem Biophys Res Commun*, 1974. **60**: 1351-1356.

53. Gewirtz, G., Schneider, B., Krieger, D.T. and Yalow, R.S., "Big ACTH: Conversion to biologically active ACTH by trypsin." *J Clin Endocrinol Metab*, 1974. **38**: 227-230.

54. Straus, E. and Yalow, R.S., "Studies on the distribution and degradation of heptadecapeptide, big, and big big gastrin." *Gastroenterology*, 1974. **66**: 936-943.

55. Straus, E., Greenstein, A.J. and Yalow, R.S., "Effect of secretin on release of heterogeneous forms of gastrin." *Gut*, 1975. **16**: 999-1005.

56. Straus, E., Urbach, H.J. and Yalow, R.S., "Comparative reactivities of 125I-secretin and 125I-minus 6-tyrosyl secretin with guinea pig and rabbit anti-secretin sera." *Biochem Biophys Res Commun*, 1975. **64**: 1036-1040.

57. Yalow, R.S., Hall, K. and Luft, R., "Immunoreactive somatomedin B in urine." *J Clin Endocrinol Metab*, 1975. **41**: 638-639.

58. Yalow, R.S., Hall, K. and Luft, R., "Radioimmunoassay of somatomedin B." *Adv Metab Disord*, 1975. **8**: 73-83.

59. Yalow, R.S., Hall, K. and Luft, R., "Radioimmunoassay of somatomedin B. Application to clinical and physiologic studies." *J Clin Invest*, 1975. **55**: 127-137.

60. Straus, E. and Yalow, R.S., "Studies on the distribution and degradation of heptadecapeptide, big, and big big gastrin." *Gastroenterology*, 1974a. **66**: 936-943.

61. Straus, E., Yalow, R.S. and Gainer, H., "Molluscan gastrin: Concentration and molecular forms." *Science*, 1975. **190**: 687-689.

62. Straus, E., Muller, J.E., Choi, H.S., Paronetto, F. and Yalow, R.S., "Immunohistochemical localization in rabbit brain of a peptide resembling the COOH-terminal octapeptide of cholecystokinin." *Proc Natl Acad Sci U S A*, 1977. **74**: 3033-3034.

63. Gewirtz, G. and Yalow, R.S., "Ectopic ACTH production in carcinoma of the lung." *J Clin Invest*, 1974. **53**: 1022-1032.

64. Ayvazian, L.F., Schneider, B., Gewirtz, G. and Yalow, R.S., "Ectopic production of big ACTH in carcinoma of the lung. Its clinical usefulness as a biologic marker." *Am Rev Respir Dis*, 1975. **111**: 279-287.

65. Yalow, R.S. and Gross, L., "Radioimmunoassay for intact Gross mouse leukemia virus." *Proc Natl Acad Sci U S A*, 1976. **73**: 2847-2851.

66. Yalow, R.S. "Nobel Autobiography." *Nobel Prize Awards, 1977*. Stockholm, Sweden.

(Intentionally Blank)

Section IV. The Roaring Sixties
1960-1967

(Intentionally Blank)

Chapter 12. The Intramural Research Program, 1960-1967

Most of the 1960s was characterized by the rapid growth of medical research within VA, and institutional recognition that VA's research efforts deserved and had earned solid agency support. Congress provided increased budget allocations, dedicated space was built or otherwise provided, and basic science was gaining a foothold. The agency's ties to academic institutions were gaining strength, as well. VA's reputation for engaging in productive clinical studies was attracting additional ties for collaborative research even as less formalized joint efforts continued with renewed vigor. The era also brought about recognition of VA research achievement, and the annual research conference continued to be an important medium for the presentation of scholarly and clinical information.

Growth of the VA research program

At the decade's start, the VA medical research program was experiencing a growth spurt. A $17 million budget supported over 6,000 projects, most of them in clinical research: 1,400 were related to neuropsychiatric disorders, 300 to tuberculosis, and the rest included almost every field of medical research.[1]

The 1960 annual report to Congress provided this definition of the agency's medical research program:

> "For the purposes of the mission of the Research Service of the Department of Medicine and Surgery of the Veterans' Administration, medical research is defined as any study undertaken to test a hypothesis related to the etiology, pathogenesis, natural history, prevention, amelioration, or cure of human disease or deformity."[2]

The report laid out the basis upon which a VA with a strong research program was able to achieve and maintain a higher standard of medical care:

1. Attraction of top-caliber staff
2. Improved clinical interest of nonresearch staff
3. Newer and better care for patients
4. Availability of expert consultation
5. Increase in prestige[3]

> "Research in the VA system is considered a privilege," the report noted. "Any member of a VA hospital professional staff who is eager to do research presents his project as a proposal in competition for funds and space with other staff members. Because VA physicians participate in research only as it relates to their patient care responsibilities, it is evident that their research originates in the clinical problems which confront them at the bedside. Probably there can be no better direction of medical research than this."[4]

The report made a strong case for providing adequately equipped laboratories to support research programs, pointing out that, in a recent year, 80 medical schools provided over $40 million for development of basic research laboratories, which allowed faculty members to

obtain an additional $65 million in federal grants. The physical plant was still the most pressing problem facing the VA research program.[5]

By this time, there was a growing body of basic research, only indirectly influenced by patient-care needs, in the VA research program. Nevertheless, the needs of the Veteran patient continued to be a major motivation for VA researchers. For example, the development of the technique of radioimmunoassay, described in the previous chapter, required elegant, complex understanding and methodologies of basic science, but the impact on patient care proved to be enormous.

New Central Office leadership

The expanding budget started during Martin M. Cummings, M.D.'s time as Director, and the resulting opportunity for innovation, attracted well-qualified leaders to the Central Office Research Service.

Marc J. ("Jim") Musser, M.D.

In 1959, Dr. Musser replaced Dr. Cummings as Director, Research Service. Musser had previously been Professor of Medicine at the University of Wisconsin, where he knew Dean Middleton well, and also Chairman of the Department of Medicine at Baylor University in Houston. He brought to the Research Service a rich network of friends in academic medicine and considerable political acumen and administrative talent. In 1962, he became Assistant Chief Medical Director/Research and Education (ACMD/R&E), but left Central Office in 1965 to direct a Regional Medical Program in North Carolina. He returned to Central Office as Chief Medical Director at the end of 1969 and continued to champion the research program while leading the VA Department of Medicine and Surgery (DM&S).

Figure 12.1. Marc J. Musser, M.D.

Benjamin B. Wells, M.D.

Dr. Benjamin Wells was appointed to the post of ACMD/R&E in the spring of 1960. He had joined VA in 1957 at the Hines (Ill.) VA Hospital and was Chief of Staff at the New Orleans

VA Hospital before coming to Central Office in July 1958 as Director of the Education Service. He held an M.D. from Baylor University and a Ph.D. in biochemistry and physiology from the University of Minnesota and was a diplomate of both the American Board of Pathology and the American Board of Internal Medicine. As a graduate student, Wells had done important research on the adrenal cortical hormones, work that was extensively cited by Edward C. Kendall, Ph.D. in his book *Cortisone*.[6] Before joining VA, Wells was Chairman of Medicine at the University of Arkansas and at Creighton University and Dean of the School of Medicine at the University of Arkansas. He had also served as a journal editor and practiced medicine with an unaffiliated group. In addition to these accomplishments, he was reported to be an expert pianist.

Figure 12.2. Benjamin B. Wells, M.D.

Dr. Wells was described by those who knew him as small in stature and huge in intellect. A witty person, he got along well with people and was a skillful politician who spearheaded VA's success in improving the research budget through the 1960s.

His sense of humor pervaded even official documents. The following passage in the fiscal year 1961 annual report to Congress was probably his:

> "The last annual report differed from most of the earlier numbers by the omission of the abstracts written by each investigator describing his research. These abstracts added little light and much bulk, so were abandoned."[7]

In the *Research and Education Newsletter*, he stated:

> "The NEWSLETTER is not 'staffed out.' For those who may be new in the business, this is the process of intellectual emasculation in which a document is passed through several hands and several echelons until it emerges in depersonalized and inanimate form, its wordage increased but its stimulating force reduced to an amplitude of zero."[8]

On another occasion he wrote:

> "Perhaps it is all wrong, but society is not willing to give money for unidentified or undisclosed ventures. The fact that scientists find research an entertaining and gratifying way of life has little persuasive value."[9]

In 1962, Dr. Wells left Central Office to become the founding Dean of the California College of Medicine at Los Angeles (now the School of Medicine at the University of California, Irvine). In a parting tribute, Dr. Musser wrote:

> "Certainly, in his quiet and gentle, yet refreshingly positive, way, Ben Wells had become one of the most respected and effective executives in the Department of Medicine and Surgery."

Wells returned to Central Office again as ACMD/R&E in 1965 when Musser went to North Carolina. A year later, Wells left once more to direct the Regional Medical Program in Alabama and then returned in 1969 as Deputy Chief Medical Director under Musser.

James A. Halsted, M.D.

Dr. James Halsted came to VA Central Office (VACO) in 1964 as Deputy ACMD/R&E. A graduate of Harvard Medical School, he had been in private practice before World War II. During the war, he served in North Africa and Italy. He began his VA career at the Wadsworth (Los Angeles) VA Hospital, where he was Chief of Gastroenterology from 1950 to 1955. There, he married Anna Roosevelt, daughter of President Franklin D. Roosevelt.[10,11]

Later he moved to the Syracuse VA Hospital, was a Fulbright scholar for two years in Iran and then Director of Postgraduate Education of the University of Kentucky Medical School. At the time of his recruitment to VACO, he was Associate Chief of Staff for Research and Education (ACOS/R&E) at the Dearborn (Mich.) VA Hospital and professor at Wayne State University.

Figure 12.3. James A. Halsted, M.D.

Dr. Halsted had become interested in medical research during World War II while stationed in North Africa. He and his colleagues studied soldiers who developed peptic ulcers under the stress of battle. They demonstrated that these were exacerbations of preexisting ulcers and that new ulcers seldom resulted from battle stress.[12] While at Wadsworth, he and his colleagues studied the absorption of Vitamin B12, demonstrating its complete absence after total gastrectomy.[13, 14] He also showed that antibiotic treatment in "blind loop syndrome" reversed the malabsorption of Vitamin B12 seen in this condition.[15, 16] While at the Syracuse VA Hospital, he demonstrated protein loss from the stomach in Menetriere's disease[17] with fellow researcher Kenneth Sterling, M.D. While in Iran, he and Ananda Prasad, M.D., later ACOS/R&D at the Allen Park (Mich.)VA Hospital, became interested in a group of dwarfs who had anemia and no sexual development. Eventually, they established zinc deficiency as the cause of this syndrome.[18] In March 1966, after two years in Central Office, Dr. Halsted moved to the Washington (D.C.) VA Hospital, where he was ACOS/R&E and VA-wide coordinator for research in nutrition.[19]

Edward Dunner, M.D.

Dr. Edward Dunner had been in VA since 1941 as a staff physician at the Palo Alto, San Fernando and Livermore hospitals in California. While at Livermore, he participated in the original tuberculosis trials under John Barnwell, M.D. (Chapter 5). From 1950 to 1954, he was Area Chief for Tuberculosis in St. Louis. He came to Central Office Tuberculosis Service in 1954 and served as Chief of Tuberculosis Research and Executive Secretary of the VA-Armed Forces Chemotherapy of Tuberculosis Cooperative Study from 1956 to 1958. In 1958, he joined the Central Office Research Service as Associate Director and Chief of the Clinical Studies Division. He was Director of the Research Service from 1962 to 1966, when he became Special Assistant to ACMD/R&E Dr. Benjamin Wells.[20]

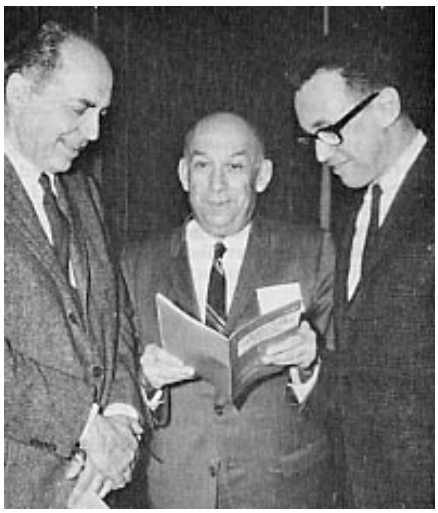


Figure 12.4. At the 1965 Annual Research Conference: Edward Dunner, M.D., center, with Ludwig Gross, M.D., of the Bronx VA Hospital and Lucien Guze, M.D., ACOS/R&E at the Los Angeles Wadsworth VA Hospital

Local research management

By 1960, governance of the research program had stabilized. Each VA hospital with a research program had a Research and Education (R&E) Committee responsible for evaluating and approving staff research proposals and distributing the support money allocated by Central Office. Each hospital received a basic institutional research allocation to provide equipment, supplies, technical support, and other facilities necessary for the proper pursuit of research activities. When a research project was completed, R&E Committee approval was needed before results could be published. The Committee comprehensively reviewed the hospital's research program annually for quality and productivity and reported findings to Central Office. The position of "Assistant Director of Professional Services for Research"(ADPSR), renamed the "Associate Chief of Staff for Research and Education" (ACOS/R&E) in 1961, was established as Secretary to the R&E Committee and as full-time coordinator of the research program.[4]

Professional papers had required Central Office approval before submission for publication until 1957, when the review and approval responsibility moved to the R&E Committees. Two copies of published papers were sent to Central Office, a practice that continued into the 1970s.[21]

Special Laboratories

In 1960, while the majority of the research carried out in VA laboratories was controlled by the R&E Committee, there continued to be Special Research Laboratories (Appendix VI), some of them new and others dating back to the 1950s. These laboratories were still controlled directly by Central Office Research Service, with budgets earmarked and activities supervised by Central Office staff. By 1963, 22 laboratories were directly supervised by Central Office staff and carried out special projects in response to Central Office direction. However, in most cases, these were investigator-directed laboratories that functioned very much like program project grants, with a central theme but a number of projects initiated by the laboratory staff.

Radioisotope program

By 1960, radioisotope research at the local level had been completely integrated into the overall research program, and the hospital Radioisotope Committee was now a subcommittee of the R&E Committee. The Central Office now considered most research projects in the Radioisotope Services in relation to disease state or research problem, rather than the use of radioisotopes. Only 185 of the 6,569 research projects listed in the 1960 annual research report were classified as "radioisotope, not elsewhere classified."[22]

Extra-VA research funding

VA investigators successfully used the privilege achieved in 1954 to apply for non-VA monies

through affiliated medical schools. Research grant support in 1960 was listed as $4.5 million for 717 projects.[23] VA was responsible for approximately one-third of the National Cancer Institute's nationally integrated cancer chemotherapy research program.[24]

Epidemiology and biostatistics

A new division of Central Office Research Service, the Geographic Epidemiology Division, was activated in July 1959. Sir Donald Acheson, KBE, who later served as Chief Medical Officer of the United Kingdom and was knighted by Queen Elizabeth, was its first Chief. After Acheson left VA in January 1960, Clifford A. Bachrach, M.D., was appointed to succeed him. The Geographic Epidemiology Division was charged with using VA materials and resources to study geographic distribution of diseases. Early efforts focused on multiple sclerosis, regional ileitis, ulcerative colitis, and nonspecific lung diseases.[25] By the mid-1970s, this division had become the only branch of the Central Office actually carrying out research.

In addition, a Central Office Research Statistics Division was established in 1959, apparently by transferring staff from the VA Controller's Office. Dr. Bachrach was also chief of this division, which included four other statisticians.[26] Many but not all of the cooperative studies received statistical support and coordination from this division. In 1962, Dr. Bachrach volunteered for service in Israel, and Donald V. Brown, Ph.D., of the Systems Development Corporation was recruited to head this Statistical Division with special responsibility for the new Research Support Centers.

The Cooperative Studies Program

In 1960, the tuberculosis and psychopharmacology studies (Chapters 4 and 8) were very active. A Tuberculosis Cooperative Study Laboratory in Atlanta was by then operating as a central laboratory serving several new tuberculosis cooperative studies. This laboratory distributed standardized testing materials to all tuberculosis cooperative study units to improve comparability of test results. In addition, cooperative studies were started to research a variety of other medical problems. The hypertension study group (Chapter 9) published its first major report in 1960.

During the early 1960s, individual program chiefs directed cooperative studies. However, Lawrence W. Shaw, who came to VA Central Office in 1963 as a senior statistician, gradually worked into overall leadership of cooperative studies. [27,28] In 1966, the first meeting was held of the Cooperative Studies Evaluation Committee (CSEC), a general advisory committee for all cooperative studies. This Committee is still active today (Appendix VII). The first CSEC chairman was William Tucker, M.D., Director of the Medical Service in VA Central Office. During the 1960s, CSEC reviewed most of the VA cooperative studies except the psychiatry studies, coordinated by the Central Neuropsychiatric Research Laboratory (CNPRL) (Chapter 8), and those studies conducted in collaboration with the National Cancer Institute, which were reviewed by committees of the National Academy of Sciences (Chapter 4).

Publications

In 1960, a publication titled *Research and Education (R&E) Newsletter* debuted and continued to be published two to six times a year through 1968. The *Newsletter* and annual reports to Congress required a more formal publications process. Thus, in 1960 the position of Publications Editor was established—a position first located in the Research Service and later moved to the ACMD/R&E office. The initial Publications Editor was Mrs. L. Tracy Fetta, who had prepared a prospectus on research in aging. She prepared the 1959 and 1960 annual reports to Congress and the *R&E Newsletter*. However, Dr. Chapple (Chapter 7) played an active role in establishing the *Newsletter* and served as its editor.[29] He was officially designated Chief of Research Publications from 1962 to1964. In addition to the annual report to Congress, titled *Medical Research in the Veterans Administration*, Research Service published occasional manuals and monographs (Appendix VII).

Budgetary management

Budgetary decision-making was generally straightforward. The Director of the Research Service had the authority to distribute research funds, and his decisions were honored. There was no advisory committee structure influencing individual decisions and there existed few bureaucratic "hoops" to master. The Director was responsible for the results of those decisions, good or bad.

Robert Efron, M.D., described his own experience with the way things sometimes worked, from the occasion when Marc J. Musser, M.D., recruited him to work for VA:

> "Efron had been working in his basement laboratory at the Medical Research Council (MRC) in London when Musser (then Director of the VA Research Service) was visiting the facility. His British hosts asked Musser if he would like to meet their young American scientist.
>
> After hearing about Efron's research, Musser asked him whether, when he came back to the U.S., he would like to work for VA. He said to contact him when the time came. Not long afterward, Efron was recruited by Boston University Medical School to do patient care and research located in the Boston VA Hospital.
>
> "Efron's lab equipment at MRC was specialized to his work, and it was decided that he could take it with him to the U.S. The delicate equipment required a huge, room-sized crate and very careful handling. He contacted Musser, and inquired whether VA might be able to pay for the crating and moving cost.
>
> "The VA research chief simply said it would be done. With no further action on the Efron's part, no supply forms, no applications, no paper work at all... the crating and shipping were accomplished. When the equipment was set up in his new VA lab, not a single item had been damaged."[30]

Introduction of Program Chiefs

The 1960 National Academy of Sciences report on the VA research program (Chapter 7) advised expansion of the Central Office professional staff. This advice, together with Dr. Middleton's support for the research program and Drs. Musser's and Wells's energetic leadership, led to a marked expansion of the Central Office research staff during the 1960s.

The concept of the Program Chief (Table 12.1) was introduced in this staffing expansion. Dr. Chapple, already responsible for the Research in Aging Division, became Chief of Research in Aging; and Lyndon Lee, M.D., already administering surgical cooperative studies (Chapter 13), became Chief of Research in Surgery. Graham Moseley's position was redesignated as Chief of Research in Radioisotopes, and Joe Meyer, Ph.D., became Chief of the Research Laboratories Division, and later (in 1962) Chief of Research in the Basic Sciences. The first recruits specifically to the position of Program Chief were Samuel C. Kaim, M.D., who arrived in 1960 as Chief of Research in Psychiatry and Neurology, and Harold W. Schnaper, M.D. and H. Elston Hooper, Ph.D., who in 1961 became Chiefs of Research, respectively, in Internal Medicine and Psychology. Later in the 1960s, recruitment continued of subject matter specialists to administer their particular areas of research, with 19 new recruits between 1963 and 1971.

Table 12.1. Program Chiefs

Lee, Lyndon E., Jr., M.D., Coordinator, Research in Surgery, 1957-1964
Chapple, Charles C., M.D., Chief, Research-in-Aging Division, 1958-1962
Moseley, A. Graham, Chief, Radioisotope Division, Research Service, 1958-1967
Kaim, Samuel C., M.D., Chief, Research in Psychiatry and Neurology, 1960-1970
Hooper, H. Elston, Ph.D., Chief, Research in Psychology, 1961-1965
Schnaper, Harold W., M.D., Chief, Research in Internal Medicine, 1961-1967
Meyer, Joe, Ph.D., Chief, Research in Basic Sciences, 1962-1968
Cass, Jules S, D.V.M., Chief, Research in Laboratory Animal Research and Care, 1963-198?
Feldman, W.H., D.V.M., Chief, Laboratory Research in Pulmonary Diseases, 1963-1967
Matthews, James H., M.D., Chief, Clinical Research in Pulmonary Diseases, 1963-1968
Filer, Richard N., Ph.D., Chief, Research in Psychology, 1965-1970
Rosenberg, Charles A., M.D., Chief, Research in Endocrinology and Metabolism, 1965-1968
Wolcott, Mark W., M.D., Chief, Research in Surgery, 1965-1970
Chauncey, Howard W., D.M.D., Chief, Research in Oral Diseases, 1966-1971
Nadel, Eli M., M.D., Chief, Research in Pathology and Laboratory Medicine, 1966-1968
Simons, David G., M.D., Chief, Research in Physical Medicine and Rehab., 1967-1971
Dury, Abraham, Ph.D., Chief, Research in Basic Sciences, 1968-1972
Cady, Allen B., M.D., Chief, Research in Gastroenterology, 1969-1971
Christianson, Lawrence G., M.D., Chief, Research in Neurology, 1969-1970
Hine, Gerald G., Ph.D., Chief, Research in Nuclear Medicine, 1969-1973
Loudon, Robert G., M.B., Ch.B., Chief, Research in Pulmonary&Infectious Dis., 1969-1970
Meyer, Leo M., M.D., Chief, Research in Hematology, 1969-1970
Oliner, Leo, M.D., Chief, Research in Endocrinology and Metabolism, 1969-1971
Adler, Terrine K., M.D., Chief, Research in Pharmacology, 1970-1972
O'Reilly, Sean, M.D., Chief, Research in Neurology, 1971-1972
Sisk, Charles W., M.D., Chief, Research in Arthritis and Rheumatism, 1971-1972

Program Chiefs were responsible for encouraging and coordinating research in their specific program areas. Each was allotted a portion of the total research budget, over which he or she had almost complete discretion. Typically, they traveled extensively, visiting laboratories and reviewing research in their program areas. They formed Research Program Committees to

assist them in directing their efforts, and they also coordinated special Study Groups. They served as coordinators of the Clinical Investigator Program within their special areas and later of the Research Associate, Medical Investigator and Research and Education Trainee programs. In their fields, they served as Executive Secretaries of the Coordinating Committees for Cooperative Studies and later as Executive Secretaries of the Program Evaluation Committees.

Research Program Chiefs (1960-1968)

Lyndon E. Lee, Jr., M.D.

Dr. Lyndon Lee came to Central Office in 1957 as Coordinator for Surgical Research within the Surgery Service. He graduated from Duke University School of Medicine in 1938 and completed postdoctoral training in surgery. Before coming to Central Office, he had wide experience in surgery, both in clinical practice and research. In 1958, when Theodore B. Moise, M.D., left the post of Chief of Extra-VA Research, Lee transferred to Research Service. He and Dr. Barnwell negotiated with the Director of the National Cancer Institute (NCI) to initiate a joint program of research on cancer therapy. Lee was responsible for coordinating this joint VA-NCI research. He also continued to coordinate research in surgery and in 1963 became Program Chief in Research in Surgery. In 1964, he left the Research Service to become Director, Surgery Service, but returned as Acting ACMD/R&E in 1970. In 1971, he became ACMD for Professional Services. Until he left Central Office in the late 1970s, he coordinated the joint VA-NCI research program, taking it with him as he went from post to post.[31]

Figure 12.5. Lyndon Lee, M.D.

Figure 12.6. Samuel Kaim, M.D., right, with Edward Dunner, M.D.

Samuel C. Kaim, M.D.

Dr. Samuel Kaim came to Central Office Research Service in 1960 as Program Chief in Psychiatry and Neurology. A New Yorker, Kaim had done his undergraduate work at Western Reserve College (now Case Western Reserve University) and studied medicine in Zurich,

Switzerland. He had been in the private practice of psychiatry until 1950, when he joined the staff of the VA hospital at Coral Gables (Fla.), where he became Chief, Psychiatry and Neurology Service, in 1958.[32]

H. Elston Hooper, Ph.D.

Dr. Hooper (Figure 16.2) was appointed Chief, Psychology Research, in 1961. After obtaining his bachelor's degree at UCLA in 1942, he served for more than three years in the Air Force as a research psychologist in the Air Crew Selection Program. He then entered the VA Clinical Psychology Program and received his Ph.D. from USC in 1950. He was staff psychologist at the Long Beach (Calif.) VA Hospital from 1950 to 1960. He then went to the Augusta (Ga.) VA Hospital to serve as Chief of the Central Research Laboratory for the Psychological Research Program for a year before going to VACO.[33] Except for a brief period in the mid-1960s as Chief of the Western Research Support Center at the Sepulveda (Calif.) VA Hospital, Hooper remained in Central Office Research Service until his retirement in 1978.

Harold W. Schnaper, M.D.

Dr. Schnaper was recruited to Central Office as Program Chief, Research in Internal Medicine, in 1961. Previously, he worked with Edward Freis, M.D., at the Washington (D.C.) VA Hospital, serving as his Assistant Chief and an active partner in the early hypertension studies (Chapter 9). In 1965, Schnaper became Assistant Director of Research Service but also continued to coordinate research in internal medicine until he left Central Office to become a professor at the University of Alabama in 1966. He was Acting Director of the Research Service after Dr. Dunner transferred to the ACMD office and before Lionel M. Bernstein, M.D., Ph.D. arrived in Central Office.[34]

James H. Matthews, M.D.

Dr. James Matthews came to the Central Office in 1961 as Secretary to the Committee on the Chemotherapy of Tuberculosis, which was then still a part of Professional Services. He had been a pulmonary specialist at the Oteen VA Hospital in Osteen, N.C., and had participated in the tuberculosis cooperative studies. From the time of his arrival in Central Office, he coordinated his activities closely with Research Service and by 1963 had transferred to Research Service as Program Chief for Clinical Research in Pulmonary Diseases. He gradually took on other responsibilities as well, becoming Chief of Research Communications in the ACMD office in 1965 and Assistant Director, Research Service, in 1968. In 1972, he left VA to head the tuberculosis control program for the State of Virginia.[35, 36]

Figure 12.7. James Matthews, M.D.

Lewis W. Carr, D.S.W.

Dr. Lewis Carr became Program Chief, Social Work Research, in 1963. His responsibilities were to develop, promote and administer the social work research program, in response to a recommendation by an Ad Hoc VA Social Work Research Committee. Dr. Carr, a Doctor of Social Work from Washington University, was Clinical Social Worker in the Mental Hygiene Clinic at VA Regional Office, St. Louis, from 1957 to 1959 and Research Social Worker at the Houston VA Hospital and Assistant Professor of Social Work in the Department of Psychiatry, Baylor University, from 1961 to 1963. At the time of his appointment, he was a member of the National Association of Social Workers, the Academy of Certified Social Workers, the Council on Social Work Education, and the National Conference on Social Welfare.[37]

Charles A. Rosenberg, M.D.

Dr. Charles Rosenberg came to Central Office as Chief of Research in Metabolism and Endocrinology in 1964 from the Batavia (N.Y.) VA Hospital, where he had been Chief of Medicine and had established a Radioisotope Unit. Previously he was at the Nashville VA Hospital as Assistant Chief of Medicine and Chief of the Radioisotope Unit. In addition to endocrinology, Dr. Rosenberg took on responsibility for coordinating research in gastroenterology and hematology, taking some of the load from Dr. Harold Schnaper.[38] Dr. Rosenberg later became Director of Medical Service in Central Office and then Chief of Staff at the Miami VA Medical Center.

Figure 12.8. Charles Rosenberg, M.D.

Mark W. Walcott, M.D.

Dr. Walcott, who had been Chief of Surgery at the Coral Gables (Fla.) VA Hospital, was Program Chief of Research in Surgery from 1964 to 1970. He took over this assignment when Dr. Lyndon Lee became Director of Surgery Service in Central Office. Lee, however, continued to be Chief of Extra-VA Research, a position in which he coordinated the NCI-funded VA surgical adjuvant studies and cancer research ward at the Washington VA Hospital.

Walcott was an active researcher and while in Central Office set up a hyperbaric oxygen chamber for mice at the Washington VA Hospital, where he carried out research on gas gangrene. He also practiced surgery at the hospital once a week. Such activities were encouraged. Hal Engle, M.D., the CMD during Walcott's later years in Research Service and a strong supporter of the VA research program, envisioned the possibility of academic affiliations for the Central Office DM&S, with close ties to the Washington VA Hospital.

Walcott was later Chief of Staff at the Salt Lake City VA Hospital and set up the Regional Medical Education Center there. He was ACMD for Professional Services during the 1980s.[39]

Figure 12.9. Mark Walcott, M.D., center, with Joe Meyer, Ph.D., and Lyndon Lee, M.D., at the 1965 Research Conference

David G. Simons, M.D.

Dr. David Simons became Program Chief of Research in Physical Medicine and Rehabilitation in 1965. He was a 20-year Veteran of the Air Force, and Director of the Physiometrics Research Laboratory at the Houston VA Hospital. In 1962, he received the Aerospace Medicine Honor citation from the American Medical Association. He continued to be based in Houston but frequently traveled to Washington.[40]

Figure 12.10. David G. Simons, M.D.

Figure 12.11. Margaret M. Plymore, Ph.D.

Margaret McCrindle Plymore, Ph.D.

Dr. Margaret Plymore became Chief, Research in Clinical Nursing, in 1965. Her office was located in the Boston VA Hospital, rather than Central Office. A sociologist by training, she had been on the faculties of Yale and Emory Universities before joining the Boston VA Hospital as its Chief Research Clinical Nurse.[40]

Howard W. Chauncey, Ph.D., D.M.D.

Dr. Howard Chauncey became Program Chief of Research in Oral Diseases on October 1, 1965. His Ph.D. degree was in biochemistry from Boston University and his dental degree from Tufts University. He had been active in dental research at Tufts, where he was Professor of Oral Pathology. Dr. Chauncey remained in Central Office until 1971, when he became ACOS/R&E at the Boston VA Outpatient Clinic.[41]

Figure 12.12. Howard W. Chauncey, Ph.D., D.M.D.

Figure 12.13. Eli M. Nadel, M.D.

Eli M. Nadel, M.D.

Dr. Nadel joined Research Service in 1965 as Program Chief, Research in Pathology. Before coming to Central Office, he had been a career physician at NIH, most recently as Chief of NCI's Diagnostic Research Branch.[41] He left VA in 1970.

Abraham Dury, Ph.D.

Dr. Dury had worked on the endocrinology of aging at the Pittsburgh VA Hospital and had chaired VA's advisory committee on research in aging. He then moved to NIH, into the new Institute for General Medical Sciences. When Dr. Joe Meyer decided to return to the laboratory in 1968, he persuaded Dury to move to VA to replace him as Program Chief, Basic Sciences. Dury stayed in VA Central Office as an important member of Research Service during the changes of the following years, until he retired in 1976.

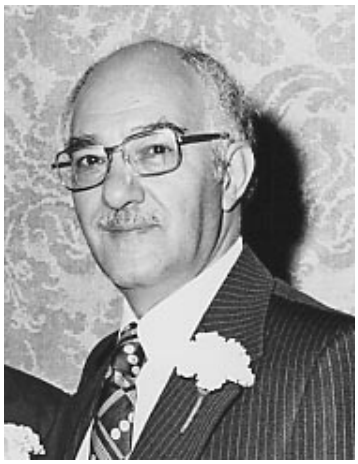


Figure 12.14. Abraham Dury, Ph.D.

Lawrence G. Christianson, M.D.

Dr. Lawrence Christianson was Director of the Automatic Data Processing Staff when he was

recruited to be Chief of Research in Neurology in 1969. He had been at VA Hospital in Fort Meade, S.D., before coming to VACO in February 1961 as Assistant Director, Medical Services. He spent only seven months in Research Service before returning to Medical Service.[42]

The Enhanced Career Development Program

In June 1961, the Clinical Investigator Program, which until then had been coordinated by Research Service's sister Education Service, was officially transferred to Research Service. Dr. Schnaper coordinated awards in internal medicine and Dr. Lee in surgery. As new Program Chiefs arrived, they assumed coordination in their areas.

The Clinical Investigator program continued to be very active during the 1960s. As of February 1962, 47 awardees had completed their appointments. Forty of them remained in academic medicine, 15 in medical schools and 25 within VA.

Shortly after they arrived, Drs. Kaim and Hooper established entry-level Research Associate programs in psychiatry and psychology to alleviate the shortage of psychiatrists and psychologists adequately trained in research. The training was one year for psychiatrists and two years for psychologists. The first Research Associates, three in psychiatry and four in psychology, entered their training in 1962.

The Research Associate in Psychology program continued as a two-year program through the 1960s. The one-year Research Associate program was later extended to include oral diseases, podiatry and pathology, areas perceived to have major shortages of qualified research personnel. In these four programs, 13 Research Associates completed training during fiscal year 1965. In many cases, the one-year appointments were extended for a second year and the Research Associate appointment soon became established as a two-year appointment. By 1967, 38 appointees participated in the physician Research Associate Program and applicants from all specialties were considered.

The early 1960s was a period of expansion of the Senior Medical Investigator (SMI) program. The VA research program had now matured to the point where many distinguished research physicians provided leadership. Appointment as an SMI conferred high honor on selected distinguished investigators in the VA hospital system. They worked independently on research of their own choosing. While they were permitted teaching and patient-care responsibilities, the major focus was to be on research activities, and they were supported directly from research funds. Their four-year appointments were usually renewed after review, so this program conferred an unusual amount of continuity for the recipient.

Dr. Musser, as Director of the Research Service, actively expanded the SMI program. Drs. Samuel Bassett (Chapter 3) and Edward Freis (Chapter 9) were appointed in 1959; Drs. Oscar Auerbach (Chapter 10) and Ludwig Gross (Chapter 3) in 1960; Dr. Jay Shurley in 1961; Dr. Morton Grossman (Chapter 7) in 1962; and Dr. Solomon Berson (Chapter 11) in 1963. Dr. Bassett died in 1962, leaving six active SMIs.

Jay Shurley, M.D., the only psychiatrist to hold an SMI appointment, had an eclectic research program. He had authored a 1948 VA *Medical Bulletin* on insulin shock therapy[43] and was engaged in research on sensory deprivation at the time he received the SMI appointment.

Figure 12.15. Jay Shurley, M.D.

Dr. Shurley's primary research interest involved the physiological, psychological and behavioral effects of unusual environments. He conducted extensive studies of the effects of sensory isolation through water immersion and other controlled environments.[44, 45] He found that patients with insomnia were helped by use of an air-fluidized bed originally developed for burn victims.[46] In the late 1960s and 1970s Dr. Shurley studied the effects of the extreme environment at the Navy's South Pole Station.[47, 48] Much of this work focused on changes in sleep patterns.[49-51]

External advisors to VA research

The Committee on Veterans Medical Problems of the National Academy of Sciences (Appendix IIc) continued into the 1960s, but its advice was limited to negotiations with other agencies, industries and universities. At the start of 1960, four VA advisory committees advised the Research Service: the Advisory Committee on Research, begun in 1955 (Appendix IIe); the Advisory Committee on Radiobiology and Radioisotopes, begun in 1947 (Appendix IId); the Advisory Committee on Problems in Aging, begun in 1955; and the committee reviewing applicants for Clinical Investigator appointments, first called the Committee on Clinical Investigations and later the Research Career Development Committee (Appendix IIj). In 1960, the first three of these committees were abolished, and a new Advisory Committee on Research was established, with membership from the three committees and other experts from outside VA to advise on all aspects of the research program. This Advisory Committee on Research (Appendix IIf) remained active until 1968.

Internal advisors: the Research Program Committees

In November 1960, Research Service began to establish Research Program Committees, whose members were available to advise the Director of the Research Service and Program Chiefs on the status of the field and to assist in broad planning and further development of the research program in their specialties. These Committees consisted primarily of VA field researchers, with some outside consultants. Each committee had an Executive Secretary from Central Office who was the Program Chief, or a subject matter expert from another Central Office Service.[52]

In fiscal year 1964, Research Program Committees were in place for basic science, cancer, cardiovascular disease, infectious disease, oral diseases, psychiatry, neurology and psychology, and pulmonary disease (Appendix IIg).

Program Evaluation Committees

In 1964, several chairmen of the Research Program Committees were asked to develop a mechanism for review of individual investigators' research programs. As a result of their recommendations, Research Evaluation Committees were established. Each principal investigator who was identified with a VA medical research laboratory or program was asked to document the scope, purpose, progress and achievements of his or her research, to enable a critical scientific evaluation by panels of experts composed of VA and non-VA members. This program was announced in a Chief Medical Director's letter dated January 8, 1965, entitled "Evaluation of Medical Research Program." These committees reviewed brief proposals; their decisions were based on the productivity of the research or the apparent promise of the investigator. By 1968, Program Evaluation Committees had been established in 12 subject areas (Appendix IIh.).

Study Groups

In 1961, VA established "Study Groups," small groups of VA investigators who met about twice a year to discuss individual research and exchange ideas and plans for new or extended cooperative studies.[53] In 1962, these groups were active in research on epilepsies, arthritis and rheumatic diseases, coccidioidomycosis, emphysema, oral diseases, physical medicine and rehabilitation, sarcoidosis, and social work.[54] By 1964 the Study Groups on epilepsies and sarcoidosis had disbanded; new groups studied chronic bronchitis, multiple sclerosis, psychological aspects of aging, and nursing.[55] By fiscal year 1967, nine study groups were active. The emphysema and chronic bronchitis groups had disbanded. There were now groups studying endocrinology and "Restoration Centers, Intermediate Care Wards, Nursing Care Home Unit and Domiciliaries."[56] Subsequently, interest in these study groups waned. The annual reports of 1968 and 1969 listed only four groups. By FY 1973, only the group studying coccidioidomycosis remained active.[57] It continues to meet annually, now sponsored by the NIH.

Research Support Centers

In 1962, Research Support Centers were established at the Hines (Ill.), Washington (D.C.) and Sepulveda (Calif.) VA Hospitals, known respectively as the Midwestern, Eastern and Western Research Support Centers. Their charge was to provide multidisciplinary consultation and assistance in:

a. Research design, mathematical and statistical formulation
b. Data acquisition, processing and analysis
c. Storage, retrieval and transmission of scientific information
d. Education and training

As originally envisioned, the center at Hines would primarily provide statistical and computational services and the one in Washington would emphasize medical instrumentation and automatic data processing.[58]

In January 1963, the Hines Center presented the first of a series of courses for research investigators, covering problems in experimental design and applied statistical methods.[59]

In March 1964, a fourth center, the Southern Research Support Center, opened at the Little Rock (Ark.) VA Hospital. While this center had a broad mission— biochemistry, physical chemistry, biophysics, statistics and data processing, research design, psychology, bioengineering and instrumentation—its 20 staff members, including seven Ph.D. scientists, had particular expertise in instrumentation and design and construction of specialized research instruments. This Center offered courses in biomedical instrumentation and atomic medicine.[60] During FY 1966, it developed procedures for a central research instrument program and became the site for the Central Research Instrumentation Pool (CRIP).[61]

In July 1965, a new Eastern Research Support Center opened at the West Haven (Conn.) VA Hospital.[62] The Center at the Washington, D.C. VA Hospital became the location of VA's pilot Automated Hospital Information Systems (AHIS) effort, pioneering work dedicated to using computers to augment hospital information systems (Chapter 19).

In time, each support center developed special interests, while still trying to serve all of the regional needs of its researchers. By 1969, the Western Center had acquired expertise in information systems and became the site of data processing for the new Medical Research Information System. The Eastern and Midwestern Centers became leaders in biostatistics, while the Southern Center expanded its expertise in instrumentation.[63]

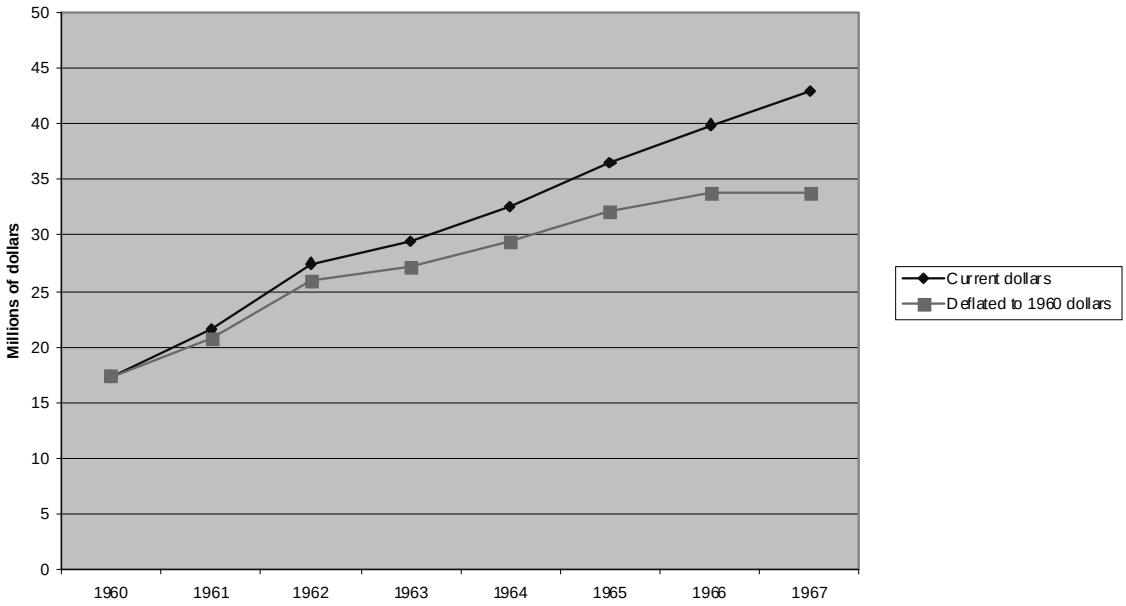
Outreach to other Federal agencies

During the 1950s and 1960s, VA actively worked with other agencies. The medical research program was and remains represented on the Councils of the National Institutes of Health. Many NIH Study Sections include VA representatives. As of 1964, VA also was represented on the President's Committee on Aging and the Committee on Scientific and Technical Information of the President's Federal Council for Science and Technology.[64]

The program expands and the budget soars

During the early 1960s, the VA research budget constantly expanded (Figure 12.16), helped by its good press and the favorable report from the National Academy of Sciences. Musser and Wells, strongly backed by Middleton, were politically very active.

Figure 12.16 Research budget, 1960-1967



The budgetary process then, as now, began with presentation and reviews of a budget through the VA hierarchy to the Bureau of the Budget, now called the Office of Management and Budget (OMB), before arriving at the Presidential budget. Within VA, the budget was reviewed by the Chief Medical Director and then the Administrator's staff. Bureau of the Budget auditors then completed a thorough review with an eye to saving money. Dr. Middleton, as Chief Medical Director, encouraged and vigorously defended growth of the research budget.[65] While his successor, Joseph H. McNinch, M.D., was less enthusiastic, Dr. H. Martin "Hal" Engle, the Chief Medical Director who followed McNinch, was also a strong advocate of research. William J. Driver, VA Administrator from 1965 to 1969, actively pushed the VA research program, even contacting the White House when necessary on its behalf.[66] Driver and Drs. Engle and Wells attended a meeting with President Lyndon Johnson to discuss federal funding of medical research (Figure 12.17).

Figure 12.17. White House meeting about federal funding of medical research

With this degree of encouragement, the research budget was consistently favorable at VA's submission stage but usually cut back by the Bureau of the Budget staff. Work at the congressional level was then necessary to restore the cuts. Here, Drs. Wells and Musser were the key players. Wells, especially, was described in interviews as a "consummate politician."

With increased resources, it was possible to expand the program as recommended by the National Academy of Sciences report. Efforts continued to build and improve the physical plant and equipment for research at VA hospitals. During the early 1960s, VA requested, and Congress appropriated, extra money for construction of badly needed VA research laboratories. Twice, the congressional appropriation had a special item for research laboratory construction. In 1961, the Research Service employed a full-time architect.[67]

VA pioneers better standards for veterinary care of research animals

Along with expanded basic science and more sophisticated clinical research programs, animal research facilities had been developed in most VA hospitals' research programs. At that time, standards for the care and use of research animals were primarily subjective. In 1962, VA appointed its first Chief of Research in Laboratory Animal Medicine and Care, Jules S. Cass, D.V.M. His charge was to develop a training program for animal care and improve the quality of research with laboratory animals.

Figure 12.18. Jules S. Cass, D.V.M.

Since 1951, Dr. Cass had been at the University of Cincinnati as Assistant Professor of Industrial Health. He received his veterinary training and M.S. degree from Ohio State University and served a fellowship in medical entomology at the College of Veterinary Medicine of the University of Minnesota, where he remained as an instructor. He also spent two years in the Communicable Diseases Center in Savannah, Ga., where he was responsible for the health of the laboratory-animal colony.[68]

Under Dr. Cass's leadership, VA developed training programs for animal technologists and set pioneering standards for veterinary care within animal research facilities. As accreditation standards developed in the general research community, VA established a policy that all animal facilities must be accredited. Dr. Cass worked very closely with animal activists, particularly groups campaigning for humane care of laboratory animals.

VA developed a reputation as a pace-setter in improving standards. Construction of animal facilities became an important part of the VA research construction program, a policy that continues to the present day.[69]

Medical research in the basic sciences

Until about 1960, most medical research in VA was carried out by clinicians and was clinical in nature. As medical science progressed, however, the scientific base for medical research became increasingly important. Collaboration and interaction with full-time, specifically trained basic scientists became very desirable.

Up to this point, most of the independent basic scientists in VA had entered through the Radioisotope Service. Since basic scientists were needed to handle the radiation safety program, from the beginning the Radioisotope Service had conferred high status on Ph.D. scientists and given them high grades in the Civil Service. However, elsewhere in medical research during the early days, the few Ph.D. scientists who entered the VA program were regarded and graded as "super technicians."[70] Largely as a result of Dr. Joe Meyer's efforts, this situation changed in the 1960s.

Joe Meyer, Ph.D.

Dr. Joe Meyer (Figure 12.9) came to VA Central Office in 1960 as Chief of the Research Laboratory Division, succeeding Harold P. Weiler, Meyer, an organic chemist by training, served as a research chemist in Chicago before World War II. During the war, he worked on programs sponsored by the Office of Scientific Research and Development and later the Manhattan Project. After the war, he worked as a chemist in the pharmaceutical industry but then went to Western Reserve College in 1946 as a graduate student and instructor in the new Biochemistry Department. He received his Ph.D. from Western Reserve in 1949 and then joined VA as Assistant Director and Principal Scientist of the Radioisotope Unit at the Denver VA Hospital, with a faculty appointment in the Department of Biophysics at the University of Colorado Medical School. While at Denver, he was in charge of the program to train public employees, such as police and firefighters, in radiation protection. In 1953, he moved to the New Orleans VA Hospital, where he installed the Radioisotope Unit and then served as its Associate Director, with an Associate Professor of Biochemistry appointment at the LSU Medical School. In 1959, he went to Houston as Chief of Medical Research Laboratories and Associate Professor of Biochemistry at Baylor University.[71]

After a short time as Chief of the Research Laboratories Division, Meyer perceived greater opportunities. The need to encourage development of basic science in the research program was recognized, and he had the background to do this. He suggested to Dr. Musser that he be made Program Chief for Basic Science, and this soon became his major responsibility. Drs. Middleton, Musser, and Wells all wanted a strong basic science component in VA and gave Meyer the autonomy he needed to achieve this goal.[70]

One of the initiatives Meyer directed was research in aging. He apparently inherited this initiative from Dr. Chapple and relied on the Advisory Committee to help him identify areas of interest. To further this work, Meyer was urged to contact the renowned scientist Linus Pauling, Ph.D., the only recipient of two undivided Nobel prizes. Meyer visited Pauling, who agreed to collaborate with a VA scientist. They recruited Arthur Chernoff, Ph.D., who had an interest in aging. Pauling was about to announce his macromolecular theory at the Sepulveda (Calif.) VA Hospital, but the arrangement collapsed under political pressure stemming from Pauling's reputation as a pacifist.[70]

Meyer, who had known Dr. Andrew Schally at Baylor University, worked with the New Orleans Hospital to recruit Schally into VA research. Meyer described his efforts to help:

> "One of the things I did was very useful to Andy. He needed all these hypothalami to work with, so Jim Musser said, 'Why don't you go up to Madison (Wis.) to the Oscar Meyer plant there and talk with them? Maybe they'll make pig hypothalami available to Andy.' So, I went up and talked with them and, sure enough, they made arrangements so we could put a technician up there. I am told... that they ended up with almost a million hypothalami, which is what made it possible for Schally to do his work."

Schally credited Meyer for making possible his Nobel Prize-winning work on the hypothalamic hormones. One of the first things he did after he won the Nobel Prize was to call Joe Meyer.

Meyer traveled extensively, pushing the importance of basic science as integral to the VA medical research program. He actively sought out distinguished and promising scientists, such as Paul Srere, Ph.D., who went to the Dallas VA Hospital, and Claude Baxter, Ph.D., who went to Sepulveda. Most of these new recruits were active academicians with appointments in affiliated universities. In addition, he encouraged promising young Ph.D.s already in the system to remain.[70]

The VA Annual Medical Research Conference

During the early 1960s, VA's popular annual research conference expanded. It was now held at the Netherlands Hilton Hotel in Cincinnati. Concurrent sections for the scientific presentations became the norm.

The Agenda Committee was bombarded with abstracts for the program. All Clinical Investigators and Senior Medical Investigators were invited and held their own special subsection meetings. The Radioisotope Chiefs continued to attend and have their own special meetings, as did the Associate Chiefs of Staff for R&E. A description of the 1963 Conference, from the January 1964 Research and Education Newsletter, follows:

> "The 14th V.A.A.M.R.C. was as successful a conference as has been held by the VA in a perceptibly long while. For the last several years, the format of these conferences has been experimental but now it seems to have settled into a proper mold. The meeting was divided, like last year's, into separate quarter-day sessions but, unlike last year's, usually it was only the format which remained constant during each of these periods. The subjects were treated with a certain continuity, although this may not have been conspicuous in any but the plenary sessions.
>
> "Tuesday evening, Clinical Investigators presented papers and Senior Medical Investigators led the discussions. Most Conferees, however, were not present but, instead, were sitting in administrative session, listening to matters discussed which touched on the specific and personal if it could be said that there was anything else at all during that evening meeting.
>
> "The first session, the official opening of the general scientific meeting, on Wednesday before the entire body, was of good omen. Its welcomes were gracious, its introductions remarkably informative of the speakers' philosophies and remarkable backgrounds and the addresses themselves extraordinarily good and well received. These last were by the William S. Middleton award winner, Stanley Ulick, M.D. of the V.A.H. Bronx and by the Chief Medical Director, Joseph H. McNinch, M.D., who was appearing before the Conference for the first time. The welcomes were by L. H. Gunter, the VA Hospital Director of the long-time host-city whose team does most of the work of the Conference, and from Dr. Jackson Freidlander, the Area Medical Director. The introductions were by the Assistant Chief Medical Director for R&E in Medicine, Dr. M.J. Musser and by one of the co-winners of last year's W. S. Middleton award, Dr. Leslie Zieve, Associate Chief of Staff, Chief of the Radioisotope Service and Chief, Special Laboratory for Cancer

Research of the V.A.H. Minneapolis, Minn. (This latter is reproduced here, in toto.)

"The second was a specialties-session during which four separate programs were conducted simultaneously in separate parlors. The largest of these was a combined medical-surgical series. The others were in psychology, pulmonary disease and the basic sciences.

"After lunch while research support (statistical and biological) was being described, about 20 large circular discs were brought into the theater-sized hall where they were set on legs, and chairs were placed around them. When this process was completed a sign, designating the topic to be discussed around it was placed on each and the round-table discussions were on their way. At one, the subject was so popular that it became clear at once that no peace or audibility would be possible around that table, so the members were led off by their leader to a parlor. At the rest of the round-tables the numbers were not so great, although still allowing little elbow-room but the enthusiasm and intensity around them had nothing to do with number and the discussions were unabated until closing time.

"Before dinner on Wednesday there was a cooperative reception. In this kind, as in the studies of the same name, the investigator can become involved to whatever degree he chooses. Nothing else was on the prescribed agenda for the evening.

"Thursday morning until the coffee break, the conferees again gathered and heard discourses as an assemblage. These were piloted by the only speaker from beyond the VA confines, Dr. Ewald Busse, Professor of Psychiatry, Medical School, Duke University, who spoke on Research in Aging and they were followed by the final period which was a second Specialties Session. This resembled the first one in all respects except that, where psychology had the front on Tuesday, psychiatry led the parlor on Wednesday. By 1:30 p.m. the 14th Veterans Administration Annual Medical Research Conference had joined the previous 13 in the cemetery for deceased Conferences and the 15th was being conceived."[72]

The Middleton Award (Chapter 7) was presented at each annual conference by the previous year's winner, and the awardee addressed the conference. After the 1960 award to Berson and Yalow, in 1961, Hubert Pipberger at the Washington (D.C.) VA Hospital received it for his work on computerization of the electrocardiogram (Chapter 13). In 1962, it went to collaborators Leslie Zieve and William Vogel at Minneapolis for their studies of phospholipids and phospholipases. In 1963, Stanley Ulick from the Bronx received the award for his work in the chemistry and metabolism of mineralocorticoid hormones. In 1964, Ulick presented it to Robert Becker for his identification of electrical control systems in living organisms, including humans.

Figure 12.19. Drs. Becker, Musser, Ulick and Wells while Dr. Becker received the Middleton Award

In 1965, Lucien Guze, M.D., and George Kalmanson, M.D. (Figure 12.20), from the Los Angeles VA Hospital received the Middleton Award for discerning the host-parasite relationship in chronic infectious kidney disease. In 1966, Guze presented the Award to Leo Hollister, M.D. of Palo Alto (Chapter 8) for his numerous significant contributions in the field of therapeutic drugs for mental illness.

Figure 12.20 Lucien Guze, M.D., and George Kalmanson, M.D., at the 1965 Middleton Award ceremony

The 1967 Middleton Award went to Leonard Skeggs, Ph.D., of the Cleveland VA Hospital for developing automated laboratory test devices, which have revolutionized laboratory medicine, and for his studies of the biochemistry of hypertension.

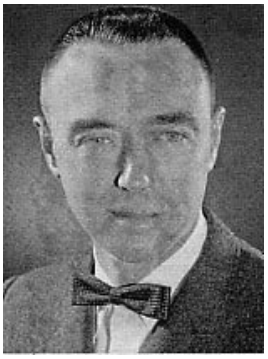


Figure 12.21. Leonard Skeggs, Ph.D., 1967 Middleton Award winner

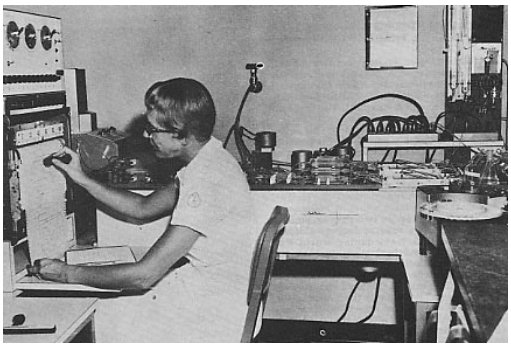


Figure 12.22. The Autoanalyzer developed by Skeggs

The Central Research Instrumentation Pool

In the early 1960s, the *Research and Education Newsletter* listed equipment that users no longer needed. Persons who wanted the equipment contacted the Research Facilities office in Central Office Research Service for equipment transfer. The success of this popular program overloaded Central Office staff. The program was transferred to Supply Service, but that did not meet the need. In 1966, VA piloted a regional exchange program under the direction of the Southern Research Support Center at Little Rock, Ark. In 1968, this expanded to the Central Research Instrument Pool, dubbed "CRIP," a nationwide instrument exchange program, that continued to be administered from the Little Rock VA Hospital. Nationwide listings of available equipment were distributed regularly, and investigators needing the equipment applied for it through their hospitals. In cases of multiple requests for an item, CRIP made a decision based on justified need.[73] Generally, preference was given to appointees in the Career Development Program. The CRIP staff also brought disabled equipment to Little Rock for repair and distribution. This equipment pool later became a resource for training biomedical engineers.

Changes in Central Office leadership

After Dr. Edward Dunner left the directorship of Research Service in 1966, Harold Schnaper, M.D., who had been his Deputy, served as Acting Director for several months, until Lionel Bernstein, M.D., from the Chicago West Side VA Hospital came into the position (Chapter 15). Shortly after Bernstein's arrival, Dr. Wells resigned as ACMD/R&E to head a Regional Medical Program centered in Birmingham, AL. Bernstein became Acting ACMD/R&E and held that position until Thomas Chalmers, M.D., was appointed ACMD/R&E in 1968.

During this period, Bernstein encouraged the Research Evaluation Committees to work toward refining the quality of VA research programs. However, it was not until after Chalmers's arrival in 1968 that, relieved of his double duty as both ACMD/R&E and Director, Research Service, Bernstein moved to implement the major changes in the program attributed to him.

The second National Academy of Sciences study

During 1966 and 1967, the National Research Council of the National Academy of Sciences again reviewed the VA research program, this time reviewing the education program as well. Their report, published in 1968, detailed the remarkable growth of the research program, both in terms of VA and non-VA monies. The number of publications from the VA research program had more than doubled between 1958 and 1966. As of FY 1966, 27 hospitals, all affiliated with medical schools, each were receiving $500,000 or more of VA medical research funds; 49 hospitals, 39 of them affiliated, were receiving between $100,000 and $500,000; and 84 hospitals, of which only 22 were affiliated, received less than $100,000. This report noted that the non-affiliated hospitals were at a disadvantage due to their remoteness from academic medical centers, but urged them to continue in cooperative and collaborative studies. It also recommended that any new VA hospitals be built in close proximity to medical schools.[74]

In its review of research management, the report describes the decentralized program. During the 1961-1966 period, institutional allocations to VA hospitals averaged 83 percent of the funds requested, suggesting that activity had been "more limited by existing investigative competence and facilities than by lack of funds."[74] The report lauds the activities of the Program Evaluation Committees that since 1965 had been reviewing individual research programs. It states: "In due course, it may be expected that all programs supported by Veterans' Administration funds will be subject to review by an evaluating committee."[74]

The 1968 NAS report reviewed the activities of the four active Research Support Centers. Some review committee members doubted that "modestly staffed and equipped centers" such as these could "deliver the wide range of services stated in their mission." In site visits, the committee members received mixed reviews about the type of help they were receiving from the Centers, because research personnel at a hospital close to a Center sought assistance more frequently than those in more remote institutions. The committee recommended,

> "That (VA) review the programs and accomplishments of its four Research Support Centers to determine whether they are accomplishing the purposes for which they were established and how their assistance to individual investigators can be enhanced."[75]

This report endorsed the Annual Research Conference, as well as the Study Groups, as excellent devices for fostering intellectual satisfaction and research interest in the staff. The report was very favorable toward the Research Career Development Program and formally recommended program continuation. Finally, in reviewing the quality of the research program, the committee once more concluded that,

> "The research program compares favorably with other broad national programs of biomedical research. It shares with them a significant quota of uninspired investigations but, on the whole, (VA) is to be commended on maintaining relatively high standards of quality of relating its program to its primary mission during a period of rapid growth."[76]

This second 1968 NAS report, with its recommendations, was both stimulus and justification for many of the changes begun in 1968.

References

1. *Medical Research in the Veterans Administration, FY 1960*. Washington, DC: Government Printing Office, 1960, 3-4.

2. *Medical Research in the Veterans Administration, FY 1960*. 1.

3. *Medical Research in the Veterans Administration, FY 1960*. 1-2.

4. *Medical Research in the Veterans Administration, FY 1960*. 5.

5. *Medical Research in the Veterans Administration, FY 1960*. 5-6.

6. Kendall, E.C., *Cortisone*. New York: Charles Scribner's Sons, 1971, 83-93.

7. *Medical Research in the Veterans Administration, FY 1961*. Washington, DC: Government Printing Office, 1961, xi.

8. *Research and Education Newsletter, July, 1960*. Washington, DC: Research and Education Office, VACO, 1.

9. *Research and Education Newsletter, July, 1965, Vol 6, 4*.

10. Telephone interview with Charles H. Halsted, M.D., son of James Halsted, M.D., March 12, 1992.

11. Telephone interview with John T. Farrar, M.D., March 26, 2001.

12. *The Harvard Medical Unit*. Finland, M. and Castle, W.B., eds.; Boston, MA: for the Countway Library, Harvard Medical School, 1983, 307-308.

13. Halsted, J., Gasster, M. and Drenick, E., "Absorption of radioactive vitamin B12 after total gastrectomy; relation to microcytic anemia and to site of origin of Castle's intrinsic factor." *N Eng J Med*, 1954. **251**: 161-168.

14. Swendseid, M., Halsted, J. and Libby, R., "Excretion of cobalt 60-labeled vitamin B12 after total gastrectomy." *Proc Soc Exper Biol and Med*, 1953. **83**: 226-228.

15. Halsted, J., "Megaloblastic anemia associated with surgically produced gastrointestinal abnormalities." *California Med*, 1955. **83**: 212-217.

16. Halsted, J., Lewis, P. and Gasster, M., "Absorption of radioactive vitamin B12 in syndrome of megaloblastic anemia associated with intestinal stricture of anastamosis." *Am J Med*, 1956. **20**: 42-52.

17. Citrin, Y., Sterling, K. and Halsted, J., "The mechanism of hypoproteinemia associated with giant hypertrophy of the gastric mucosa." *N Eng J Med*, 1957. **257**: 906-912.

18. Halsted, J.A., Ronaghy, H.A., Abadi, P., Haghshenass, M., Amirhakemi, G.H., Barakat, R.M. and Reinhold, J.G., "Zinc deficiency in man. The Shiraz experiment." *Am J Med*, 1972. **53**: 277-284.

19. *Research and Education Newsletter, March-April, 1966.* 18-19.

20. *Research and Education Newsletter, September, 1962*. 4.

21. *Research and Education Newsletter, May, 1962.* 3.

22. *Medical Research in the Veterans Administration, FY 1960*. 643-659.

23. *Medical Research in the Veterans Administration, FY 1960*. 6.

24. *Medical Research in the Veterans Administration, FY 1960*. 11.

25. *Medical Research in the Veterans Administration, FY 1960*. 28.

26. *Research and Education Newsletter, May, 1960.* 16.

27. *Research and Education Newsletter, November, 1962*. 7-9.

28. Interview with Lawrence Shaw, February 3, 1994 at Mr. Shaw's home, Gainesville, FL.

29. *Research and Education Newsletter, May, 1960.* 2.

30. Telephone interview with Robert Efron, M.D., 1988.

31. Interview with Lyndon Lee, M.D., April 7, 1988 at a restaurant in Bethesda, MD.

32. *Research and Education Newsletter, September, 1960*. Washington, DC: Research and Education Office, VACO, 28.

33. *Research and Education Newsletter, May, 1961*. 24.

34. Telephone interview with Harold W. Schnaper, M.D., January 26, 1992.

35. Telephone interview with James H. Matthews, M.D., May 25,1988.

36. Letter from James H. Matthews, M.D. to author, written at Richmond, VA, April 14, 1988.

37. *Research and Education Newsletter, November, 1963*. Washington, DC: Research and Education Office, VACO, 15.

38. *Research and Education Newsletter, February, 1965*. Vol. 6. Washington, DC: Research and Education Office, VACO, 1965, 4.

39. Interview with Mark Walcott, M.D., April 5, 1988 at VACO.

40. *Research and Education Newsletter, November, 1965*. Vol. 6. 1965, 4.

41. *Research and Education Newsletter, November, 1965*. 5.

42. Interview with Lawrence G. Christianson, M.D., May 4, 1992 at Dr. Christianson's home in suburban Maryland.

43. Shurley, J.T. and Bond, E., "Insulin shock therapy in schizophrenia." *Medical Bulletin*, 1948.

44. Serafetinides, E.A., Shurley, J.T., Brooks, R. and Gideon, W.P., "Electrophysiological changes in humans during perceptual isolation." *Aerosp Med*, 1972. **43**: 432-434.

45. Serafetinides, E.A., Shurley, J.T., Brooks, R. and Gideon, W.P., "Sensory versus perceptual isolation: a comparison of their electrophysiological effects." *Aerosp Med*, 1973. **44**: 539-541.

46. Miller, W.C., Jr. and Shurley, J.T., "Treatment of insomniac patients with the air-fluidized bed." *Am J Psychiatry*, 1972. **128**: 1147-1149.

47. Popkin, M.K., Stillner, V., Osborn, L.W., Pierce, C.M. and Shurley, J.T., "Novel behaviors in an extreme environment." *Am J Psychiatry*, 1974. **131**: 651-654.

48. Serafetinides, E.A., Shurley, J.T. and Brooks, R.E., "EEG and the effects of photic stimulation at the South Pole." *Aerosp Med*, 1971. **42**: 52-53.

49. Natani, K., Shurley, J.T., Pierce, C.M. and Brooks, R.E., "Long-term changes in sleep patterns in men on the South Polar Plateau." *Arch Intern Med*, 1970. **125**: 655-659.

50. Joern, A.T., Shurley, J.T., Brooks, R.E., Guenter, C.A. and Pierce, C.M., "Short-term changes in sleep patterns on arrival at the South Polar Plateau." *Arch Intern Med*, 1970. **125**: 649-654.

51. Natani, K. and Shurley, J.T. "Disturbed sleep and effect in an extreme environment. In: Sleep Physiology, Biochemistry, Psychology, Pharmacology, Clinical Implications." *First European Congress on Sleep Research*. Apr. Basel, Switzerland: S. Karger, Basel, 1972, 426-430.

52. *Medical Research in the Veterans Administration, FY 1961*. 12-14.

53. *Medical Research in the Veterans Administration, FY 1961*. 68-70.

54. *Medical Research in the Veterans Administration, FY 1962*. Washington, DC: Government Printing Office, 1962, 78-84.

55. *Medical Research in the Veterans Administration, FY 1964*. Washington, DC: Government Printing Office, 1964, 82-86.

56. *Medical Research in the Veterans Administration, FY 1967*. Washington, DC: Government Printing Office, 1967, 99-103.

57. *Medical Research in the Veterans Administration, FY 1973*. Washington, DC: Government Printing Office, 1974, 94-95.

58. *Research and Education Newsletter, May, 1962*. 7-8.

59. *Research and Education Newsletter, March, 1963*. Vol. 4. 13.

60. *Research and Education Newsletter, April, 1965*. 8-9.

61. *Medical Research in the Veterans Administration, FY 1966*. Washington, DC: Government Printing Office, 1966, 87.

62. *Research and Education Newsletter, April, 1965*. 9-10.

63. *Medical Research in the Veterans Administration, FY 1969*. Washington, DC: Government Printing Office, 1969, 72-78.

64. *Medical Research in the Veterans Administration, FY 1964*. 4.

65. Interview with Martin Cummings, M.D., April 7, 1988 at Dr. Cummings' office in Washington, DC.

66. Interview with Thomas Chalmers, M.D., July 29,1992 at a hotel lobby in Boston, MA.

67. *VA Telephone Directory*. Washington, DC: 1962

68. *Research and Education Newsletter, September, 1962*. Washington, DC: Research and Education Office, VACO, 7-8.

69. Interview with Jules Cass, D.V.M., May 8, 1992 at the Cosmos Club in Washington, DC.

70. Interview with Joe Meyer, Ph.D., May 4, 1992 at Dr. Meyer’s home in suburban Maryland.

71. *Research and Education Newsletter, September, 1960*. 28-29.

72. *Research and Education Newsletter, January, 1964*. 1.

73. *Medical Research in the Veterans Administration, FY 1969*. 78.

74. NAS-NRC, *Evaluation of Biomedical Research and Education in the Veterans' Administration*. Washington, DC: National Academy of Sciences, 1968, 28.

75. NRC, *Evaluation of Biomedical Research and Education in the VA*. 1968, 30.

76. NRC, *Evaluation of Biomedical Research and Education in the VA*. 1968, 34.

(***Intentionally Blank)***

Chapter 13. The VA Cooperative Studies Program of the 1960s

The Veterans' health care system is such an excellent venue for cooperative clinical trials that it is understandable that VA is often—if erroneously—credited with being the birthplace of this form of clinical research. In fact, a few cooperative studies had been performed by others even before the landmark VA tuberculosis trials (Chapter 5), and the British Medical Research Council ran tuberculosis trials at about the same time as the VA trials. It is certainly accurate to say that VA clinicians were among the first to understand the power of this important tool for evaluating and improving patient treatment, and VA clinicians have applied its methodology to many clinical problems.

In a cooperative study, investigators at different hospitals analyze a clinical problem by following exactly the same protocol and controlling as many factors as possible. Since there are inevitable differences between hospitals, even those within the VA system, the unique aspect stemming from one local environment becomes less important than it would be in a study conducted in a single hospital. Also, by working together, investigators can study many more patients affected by the condition in a shorter time than would be possible in a study limited to the patient population of a single hospital. Moreover, economies of scale make it practical to include professional coordination and statistical support.

The earliest VA cooperative studies include the tuberculosis trials (Chapter 5), the psychopharmacology studies and the predecessor study of prefrontal lobotomy (Chapter 8), the hypertension studies (Chapter 9), and the earliest of the truly randomized VA studies, evaluation of the effect of isoniazide on multiple sclerosis conducted jointly with the Follow-up Agency (Chapter 4). VA groups outside of Research Service spearheaded these early studies, but Research Service soon became involved, providing in differing degrees monetary, administrative or statistical support. By the early 1960s, the Research Service had assumed general responsibility for cooperative studies. Edward Dunner, M.D., who became Chief of the Clinical Studies Division of Research Service in 1958 (Chapter 12), transferred the tuberculosis studies to the Clinical Studies Division when he became Chief, formalizing a collaboration that had increased since the beginning of that research.

Statistical support for VA Cooperative Studies

VA Central Office statisticians who supported the early tuberculosis and hypertension trials worked for the agency's Controller's Office. In 1957, a Research Statistics Division consisting of five statisticians and headed by Clifford Bachrach, M.D., was established in that Office.

Bachrach had graduated from medical school in 1941 and served as an Army doctor during World War II. After the war, he had earned an M.P.H. degree from Johns Hopkins University, taking "all the statistics courses they offered." Subsequently, he was a Hopkins faculty member for 10 years, teaching statistics and epidemiology before joining VA. He organized a dedicated staff to begin collecting and sorting data and contributing their analyses of the clinical implications. In a 1992 interview, Bachrach described the character of working with research statistics in those early days:

> "I had a shop with about 10 or a dozen people... four of them were college graduates with some degree of training in statistics... (and there were) about seven or eight clerical people and a secretary.
>
> "The state of the art was 80-column punch (IBM) cards.... You had to write up your specifications (for a computer run) and you were behind the administrative parts of the VA in priority... a difficult way to work."
>
> In view of the administrative barriers to using the fledgling data processing equipment, Bachrach expressed a continuing affinity for the simple 3-by-5 card.
>
> "I still think (the 3 by 5 card) is a wonderful device, for a number of reasons. I have always been strong on having people rub their noses in the data. I don't like this business of putting it all into the machine and putting in a program that does an analysis of variance and getting out some things at the end, without looking at the distributions, looking at the peculiarities of the data that you see when you look at them one by one."[1]

In 1962, Dr. Bachrach left VA to accept a U.S. Public Health Service assignment in Israel. At about that time, the research statistics unit was moved to Research Service and became part of the Clinical Studies unit under Dr. Edward Dunner. Lawrence W. Shaw was recruited to the position of head statistician.

Shaw had previously been Chief of the Records and Statistics Unit in the tuberculosis program of the U.S. Public Health Service, studying the epidemiology of BCG vaccination. His initial appointment in VA was to the Research Statistics Division in Research Service, where he was to be responsible for the statistical aspects of the cooperative studies that had formerly been under Dr. Bachrach. Shaw had graduated from Ohio Wesleyan University, earned an M.S. from the University of Pennsylvania, and pursued other graduate studies at Ohio State and Columbia Universities. Prior to joining the Public Health Service in 1945, he had been a statistician with the War Department.

In the early 1960s, the source of statistical support for the Cooperative Studies Program varied markedly, depending on the type of study and investigators' preferences. Statisticians in Central Office supported the medical studies. The ongoing surgical and cancer studies used contract statisticians, based at a university or employed by the Follow-up Agency. The psychiatric studies received their planning, administrative and statistical support from the Central Neuropsychiatric Research Laboratory (CNPRL) at the Perry Point (Md.) VA Hospital.[2]

When the Research Support Centers (Chapter 12) were established, they were intended to support only individual research. However, they became sites of statistical expertise, and as time went on, the Eastern Research Support Center assumed statistical support for some of the Cooperative Studies. At the same time, the statisticians in Central Office who left were not replaced. By the end of the 1960s, the only statistician left was Shaw. His role became primarily one of coordinating studies rather than that of hands-on statistician. However, the hybrid system, with many of the

cooperative studies receiving statistical support from contractors overseen by Central Office coordinators, was well-established, and it continued into the 1970s.

Governance of a Cooperative Study in the early 1960s

Each cooperative study consisted of a chairman who was a VA clinician from one of the participating hospitals, a principal investigator at each hospital, a coordinator from VA Central Office, generally from Research Service, and a statistician. In most studies, consultants from outside VA also met with the group. Usually, an executive committee of the study's key people (the chairman, VACO coordinator, statistician and selected participants) met frequently to review results and plan future strategy. In some studies, the chairman and coordinator served this function without a committee. All participants met once or twice yearly. Decisions were made by consensus. Generally, the participants themselves made the key decisions about the direction of their study, and overall guidelines were flexible. Before 1966, no centralized or other systematic external review process existed for cooperative studies.

Funding for cooperative studies competed directly with individual research projects in a disciplinary area. Program Chiefs for the various areas of study were responsible for distributing the funds within those areas, using their best judgment as to whether a cooperative study or an individual investigator's project should receive higher priority.[3]

Cooperative Studies Evaluation Committee

In 1966, the Cooperative Studies Evaluation Committee (CSEC) (Appendix IIi) was formed. Shaw and others felt a need to establish guidance for the Cooperative Studies Program. As Shaw described it in an interview:

> "My opinion was that the evaluation of quality research in the VA had proceeded along lines where there were field committees established to advise the VA on the quality of each and every research field (the Research Evaluation Committees)... I thought that trend was very good, and it moved progressively through all domains of VA research enterprises. There was no similar thing for cooperative studies. Cooperative studies were largely influenced by the VA coordinator... but (we proposed) to set up an evaluation committee that would work with all proposed new cooperative studies and comment on the wisdom of (the plan)."

William Tucker, M.D., Director of the Medical Service and a long-time participant in the tuberculosis trials, chaired the first meeting of the CSEC on March 11, 1966. At this meeting, the group reviewed the Research Service's current structure and where the Cooperative Studies Program fit into the Service. They accepted as their charge to consider current cooperative studies and new proposals for cooperative studies in all fields of medical research and related specialties. The Director of Research Service would decide which studies were to be evaluated.

At its first meeting, the CSEC reviewed a proposal for a new cooperative study on osteoporosis. It did not approve the proposal as written but made extensive suggestions for improvement and recommended going ahead with a proposed pilot study. In this case, the pilot study did not lead to a complete study.[3] After that, the CSEC met three times a year for some time and then settled into semi-annual meetings. This Committee continues to be active in today's VA, and its

recommendations are routinely accepted as guidelines for funding new and continuing cooperative studies.

Table 13.1. VA Cooperative Studies listed in annual reports, 1960-1970

Name of Cooperative Study	Years listed
Antihypertensive agents (Chapter 9)	1956–1975
Atherosclerosis	
Cardiology section	
Anticoagulant	1957–1971
Drug cholesterol lowering	1961–1962
Drug lipid	1962–1971
Neurology section	
Anticoagulant	1957–1962
Drug cholesterol lowering	1961–1962
Drug lipid	1962–1971
Estrogen	1963–1970
Diet section	
Low fat and unsaturated fatty acids	1957–1961
Automatic cardiovascular data processing	1960–1974
Diabetes mellitus	1958–1965
Endocrine disorders	1958–1966
Functional (nonorganic) deafness	1961
Gastroenterology (gastric ulcer)	1959–1969
Hepatitis	1967–1975
Osteoporosis	1967–1969
Arthritis – ankylosing spondylitis	1968–1970
Nephrosis	1966
Aging in men	1963–1964
Endocrine morphology in aging	1965–1967
Chemotherapy in psychiatry	1957–1973
Outpatient psychiatry	1958–1964
Multiple sclerosis	1957–1963
Microbiology in multiple sclerosis: pilot study	1960–1962
Amyotrophic lateral sclerosis	1958–1961
Psychological research	1957–1962
Chemotherapy of tuberculosis	1946–1974
Chemoprophylaxis of tuberculosis	1963–1974
Pulmonary function testing	1956–1965
Coccidioidomycosis	1957–1961
Fungus diseases (blasto-, histo-& crypto-coccosis)	1957–1972
Oral exfoliative cytology	1961–1963
Hospital infections study	1956–1963
Coronary artery disease surgery	1957–1975
Parkinson’s syndrome surgery	1956–1968
Esophageal varices	1956–1975
Solitary pulmonary nodules	1957–1968
Ruptured intervertebral disk	1956–1967
Techniques for early diagnosis of lung cancer	1957–1962
Peptic ulcer surgery	1956–1972
Evaluation of analgesics	1964–1975
Peripheral vascular disease	1963–1968
Esophageal cancer	1963–1972
VA cancer chemotherapy study group	1956–1968
Lung cancer chemotherapy study group	1957–1975
VA cooperative urological group	1959–1975
VA surgical adjuvant cancer chemotherapy study	1957–1975
Infusion substudy	1963–1967
University surgical adjuvant study	1958–1963

Western cooperative cancer chemotherapy group	1961–1963
Pacific VA Cancer chemotherapy group	1961–1971
Southwest cancer chemotherapy group	1956–1964
Midwest cooperative chemotherapy group	1959–1964

Between 1960 and 1970, a total of 54 VA cooperative studies were listed in the annual reports to Congress (Table 13.1), covering a wide range of disciplines. In 1960, 34 were in progress; in 1970, 21 were in progress; 12 studies were in progress throughout this entire period.

A number of cooperative studies grew out of the tuberculosis trials (Chapter 5) and the annual conference they stimulated. These studies became independent of the tuberculosis trials themselves, though the same investigators were often involved. Among the studies included were research on the solitary pulmonary nodule, pulmonary function testing and fungal diseases of the lungs, each of which we will discuss in the next few pages.

The solitary pulmonary nodule

As part of the transition of the VA-Armed Forces studies from research specifically of tuberculosis to studies of pulmonary disease in general, the surgeons in the group began to study solitary pulmonary nodules that were discovered on routine chest X-rays. In 1957, a study of patients with such nodules began under the leadership of John Steele, M.D., of the San Fernando (Calif.) VA Hospital.

Dr. Steele died before the final 10-year follow-up period was completed, and George Higgins, M.D., and statisticians from the group at the Follow-up Agency completed the analysis. Patients included in the study were male patients with asymptomatic, undiagnosed solitary pulmonary nodules less than 6 centimeters in diameter. All underwent surgery. In this group, 370 of the lesions proved to be malignancies that could be removed. These patients were then followed for 10 years after surgery. The five-year survival was 38.5 percent and the 10-year survival 20.1 percent. Survival was longer in younger patients and those with smaller nodules. Comparing this series with a different series of VA patients who had resectable but symptomatic lung cancer, who had a 26.3 percent 5-year survival, indicated the advantage of removing the cancer before it became symptomatic.[4]

Chemoprophylaxis of tuberculosis (1963–1974)

Another study spun off from the tuberculosis trials was a trial of isoniazid in the prevention of recurrence in patients with tuberculosis in remission. This trial, based on a study that showed a significant rate of reactivation of tuberculosis in VA patients with inactive disease, was a randomized double-blind study with three regimens, two with isoniazid and one with placebo only. A total of 7,036 patients with inactive disease, including some who had received prior chemotherapy, were treated for two years and then observed for five more years. In previously untreated patients, isoniazid led to fewer reactivations than experienced by patients receiving placebo, but previously treated patients, who had a very low rate of reactivation, showed no difference.[5]

Fungal diseases

Groups from VA and Armed Services hospitals in areas endemic for systemic fungal diseases

started cooperative studies of coccidioidomycosis, histoplasmosis and blastomycosis in the late 1950s. These diseases, while rare, can pose serious clinical problems in their severe forms. The cooperative approach was the only feasible way to conduct studies with the potential to yield definitive answers about the best treatment.

Coccidioidomycosis

An example of the easy transition during the 1960s between a cooperative study and a loose coalition of persons interested in a problem involved the disease coccidioidomycosis. Especially in the Southwest and the deserts and valleys of California, where it is endemic, this disease was important in the differential diagnosis of tuberculosis and was treated by the same pulmonary specialists who treated tuberculosis. In 1957, a group interested in coccidioidomycosis met at the annual tuberculosis meetings and formed a cooperative study group. As a first step, they created a registry of patients with systemic coccidioidomycosis and began meeting annually to discuss this disease. By the early 1960s, it had become apparent that the only effective treatment, amphotericin B, was very toxic and that a randomized trial was not feasible at that time. Instead, the group became a VA Study Group and continued their annual meetings to share clinical experiences and the results of basic research.

At the 14th meeting of this group, in 1970, attendees included representatives from the VA hospitals at Fresno, Long Beach, Los Angeles, San Fernando, San Diego, Oakland and Sepulveda, Calif.; Tucson and Phoenix, Ariz.; and the Western Research Support Center and VACO. Two Army hospitals, two Air Force hospitals, the Centers for Disease Control in Atlanta, the NIH, UC Davis, USC, San Diego State University, and the Kern County, Calif., General Hospital were also represented. By this time, the group had added the sponsorship of local pulmonary professional groups to its primary VA support.[6] This group has continued to be active. The group is currently under NIH sponsorship, with VA researchers as active members and John N. Galgiani, M.D., of the Tucson VA Medical Center as Secretary.[7]

Histoplasmosis

In this study, which began in 1957 and ended in 1972, 85 patients with chronic pulmonary histoplasmosis were treated with amphotericin B, with doses randomized. Endpoints were the elimination of histoplasma from the sputum and the occurrence of amphotericin B toxicity. Both were related to dosage and duration of therapy. The relatively small dose of amphotericin B, 0.5 grams given over the course of 3.5 weeks, controlled the infection in only two-thirds of the patients. Even at this low dose, 80 percent had toxic reactions, but these did not require interrupting the treatment, and re-treatment of patients who failed to respond was uniformly successful. On the other hand, a dose of 2.5 grams given over the course of 17 weeks controlled the infection in all patients, but toxicity was reported in 86 percent of patients, and in 29 percent toxicity was so severe that therapy was discontinued. Participants in the study concluded that the best approach to using this drug was to employ a dose intermediate between the two tested, or to use a small dose followed by re-treatment when necessary.[8]

Blastomycosis

This group carried out, also from 1957 through 1972, a randomized trial comparing two potential treatments for this rather rare systemic fungal disease. Of 84 patients with North American

blastomycosis entered into the study, 41 were treated with amphotericin B and 43 received 2-hydroxystilbamidine. The results showed that pulmonary blastomycosis of a noncavitary nature, which was not extensive in its degree of involvement and was either not disseminated to other organs or disseminated only to the skin, responded well to either drug. When pulmonary involvement was extensive or associated with cavities, amphotericin B was the more effective agent. Involvement of any organ other than the lung or skin was best treated with amphotericin B.[9]

Cooperative groups developing diagnostic methods

Several groups of hospitals were involved in collaborative efforts to improve diagnostic methods. Prominent among them were the pulmonary function study, the study of endocrine disorders and the automatic cardiovascular data processing group.

Pulmonary function testing

A cooperative study between 1956 and 1965 was developed to standardize techniques and establish normal values for the multiple tests in use to evaluate pulmonary function. The research group critically evaluated tests for measuring ventilation, lung volumes and alveolar capillary diffusion and then applied them to diagnostic and prognostic studies of patients with emphysema and those undergoing thoracic surgery.

Endocrine disorders

This group of investigators at 10 VA hospitals started in 1958 with the intention of using the randomized clinical trial method to study rare endocrine diseases such as Addison's disease. However, the researchers agreed that standardization of diagnostic methods was needed first. They developed the ACTH stimulation test for diagnosis of adrenal hypofunction or hyperfunction. Based on data from over 6,000 such tests, they set the "gold standard" for these diagnoses in 1966.

By the mid-1960s, the group developed a cluster of four subcommittees that contributed technical leadership in specific areas for development of cooperative study protocols. Pilot studies evaluated the effects of human growth hormone in renal failure, obesity and osteoporosis. With help from their consultants, Drs. Berson, Yalow and Unger, [10] the research group developed immunoassays for insulin, growth hormone, parathormone, TSH and ACTH.

In 1966, this group was redesignated a "Study Group" and charged with identifying possible future cooperative studies. While such additional studies were never conducted, the contributions of this group to endocrinology were profound. The standardized ACTH test was widely used for diagnosis of adrenal disease until radioimmunoassay of the adrenal compounds became reliable. And the improved availability of radioimmunoassay of the hormones benefited millions of patients.

Automatic cardiovascular data processing

Computerization of the electrocardiogram (EKG or ECG) is now an accepted technology, assisting in the routine diagnosis of heart disease. One of the pioneers in this field was Hubert Pipberger, M.D., at the Washington (D.C.) VA Hospital. By the late 1960s, Dr. Pipberger had assembled a

group of collaborators from eight VA hospitals to collect patient EKG data using his program for automatic analysis and to advise him on improvements in the program. The following excerpts from the annual *Medical Research in the Veterans Administration* give the flavor of this work:

> 1969: "Electrocardiograms of a series of 405 patients with pulmonary emphysema of moderate or severe degree were studied. Using a variety of statistical techniques, optimal ECG measurements were determined for the differentiation of pulmonary emphysema ECG'S from normal.
>
> "They were divided into those which can be conveniently obtained through visual record analysis and those of a more complex nature obtained by digital computation. Using 14 ECG measurements with a multivariate statistical technique, more than 80 percent of the emphysema cases could be classified correctly with a false positive rate of only 5 percent. Thus, the electrocardiogram could be improved substantially as a diagnostic tool for the recognition of pulmonary emphysema which represents an increasing health hazard.
>
> "A similar study was performed on 452 ECG records from patients with ventricular conduction defects. They were divided into those with and without a history of myocardial infarction. Recognition of infarcts in the presence of ventricular conduction defects has always been a most difficult problem in electrocardiography. Using multivariate statistics more than 50 percent of the infarcts could be classified correctly. The results were confirmed in 89 autopsy cases.[11]
>
> 1974: "In long-distance telephone transmissions of electrocardiograms, excessive noise interference is frequently encountered. When records were transmitted from the VA Hospital West Roxbury, Mass. to the VA Hospital, Washington, D.C., over a three-year period, data could not be successfully processed by computer because of high noise levels in approximately 8 percent of the cases. A digital filter was designed and tested, therefore, which led to elimination of most of the interference without substantial distortions of the EGG data proper. No more records were lost after application of the filter.
>
> "Electrocardiograms from 191 patients with mitral stenosis were studied and compared with 510 records from normal subjects. Using a computer program based on multivariate analysis, it was possible to diagnose correctly 74 percent of the cases, which compared very favorably with the 44 percent recognized by conventional hand measurements.
>
> "A new computer program was developed for the diagnosis of myocardial infarcts in the presence of ventricular conduction defects. When tested on 847 patients, it was possible to identify records from patients with infarcts correctly in 61 percent of the cases."[12]

During the 1970s, Pipberger and his colleagues compared, in patients with clear diagnoses independent of the EKG, the accuracy of the computerized analysis with that of nine experienced electrocardiographers. The human interpreters had an accuracy of 54 percent, which improved to

62 percent when they were shown the results of the automated interpretation. The computer analysis was 76 percent accurate in the same cases. The superiority of computer analysis was attributed to the use of a Bayesian classification method and multivariate analysis by the computer.[13]

Analgesia and anesthesia

This 1963-1975 study involved a group of VA hospitals standardizing the effects of both new and established drugs for the relief of pain. It was led by William Forrest, M.D., an anesthesiologist at the Palo Alto (Calif.) VA Hospital and involved the cooperation of five VA hospitals. Stanford University's Byron Brown, Ph.D., was the consulting statistician. The group developed practical questionnaires to assess pain and collaborated with trained nurse observers. In general, morphine was used as the comparison standard for parenteral agents, and codeine for oral agents. This group collaborated with the National Academy of Sciences' National Research Council, Committee on Drug Addiction and Narcotics, which selected the important drugs to test, as well as with pharmaceutical companies that supplied the blinded agents. Many agents were evaluated during the course of this study. A subcommittee on animal anesthesia compiled a manual of anesthetic techniques for commonly used laboratory animals.

These researchers were pioneers in computer analysis of the complex data generated from this type of study. In 1964, they reported:

> "Statistical methods of handling the data from the participating hospitals have been refined such that rapid computer analysis is now possible. Statistical tests have been applied to the computer method and the data has been examined by several methods with consistent results showing little variability."

These methods were later used in other cooperative studies. The transition to their use was expedited by Kenneth James, Ph.D., a statistician for the analgesia studies, who later joined the Hines Cooperative Studies Program Coordinating Center and subsequently became the founding Chief of the Coordinating Center at Palo Alto.

Diabetes

From 1958 through 1965 this study examined new oral drugs to control diabetes in patients with non-insulin-dependent diabetes mellitus. Eleven VA hospitals cooperated in the randomized, double-blind study comparing chlorpropamide, tolbutamide and placebo. The patients were highly selected, with only 121 chosen out of the 3,493 screened. Chlorpropamide controlled diabetes in more patients than did tolbutamide (83 percent vs 60 percent), but both drugs were more effective than placebo (26 percent). This study, together with similar studies by others, helped establish these drugs' roles in diabetes care.[14]

Atherosclerosis

Investigators especially interested in heart disease or neurovascular disease participated in this study group.

The cardiology group focused on dietary control, and their efforts soon concentrated on a diet study in the domiciliary at the Los Angeles VA Hospital under the leadership of Seymour Dayton, M.D.

The neurology group carried out a series of studies aimed at lowering the risk of stroke in patients with cerebral atherosclerosis. Their first effort, completed in 1960, was a study of anticoagulants. Investigators in nine VA hospitals studied 155 patients with documented cerebrovascular disease, either cerebral ischemia or cerebral infarction. The patients were divided equally on a random basis between treatment and control groups and observed for an average period of about nine and 12 months, respectively, after entering the study. Although anticoagulation appeared to decrease the number of attacks of cerebral ischemia, there was no reduction in the incidence of new or recurrent strokes. A higher mortality rate was found in the treated patients, due in part to hemorrhagic complications. The study concluded that long-term anticoagulation is neither a practical nor effective method of treatment for the majority of patients with cerebrovascular disease caused by atherosclerosis.[15] An independent, NIH-supported study reported similar findings around the same time.

Next, the neurology group studied the effect of estrogens in preventing repeat stroke. Fifteen VA hospitals studied 572 men who had suffered cerebral infarctions, assigning them randomly by a double-blind protocol 1.25 mg Premarin daily, 5 mg Premarin daily or placebo. They found that estrogen administration did not reduce the incidence of cerebral infarction, transient cerebral ischemia or death due to vascular disease. In fact, the use of hormones was associated with a higher overall death rate. This was due to cancer and vascular disorders, such as pulmonary embolism, mesenteric thrombosis and heart failure and various other diseases. On the other hand, incidence of and death from myocardial infarction was decreased in treated patients compared with control patients. The investigators concluded that men with cerebral infarction received no benefit from estrogens given in moderate amounts for up to five years.[16]

Another group of 20 VA hospitals studied the effect of clofibrate, a lipid-lowering drug, in 532 patients who had suffered cerebral infarction or transient cerebrovascular ischemic attacks (TIA). In a randomized, double-blind study, patients were assigned to clofibrate, 2 grams daily, or to a placebo, and were followed for up to 4½ years. Contrary to expectations, recurrence of cerebral infarction actually increased in patients receiving clofibrate compared to controls. The incidence of new myocardial infarction and new TIA was similar in both groups. Despite the more frequent strokes in treated patients, they had a decrease in mortality, partially explained by a lower death rate from these recurrences. There was no correlation between pretreatment lipid (cholesterol and triglyceride) values and the result of therapy. Use of clofibrate, however, was associated with a slight reduction of cholesterol and a sustained fall in triglyceride levels. The investigators concluded that this was not an effective way to prevent repeat vascular insults in stroke patients.[17]

Gastric ulcer

Gastroenterologists in 16 VA hospitals studied 638 patients with gastric ulcers that were not considered to be malignant based on X-ray. Patients were hospitalized and treated with antacids and diet, the standard treatment for peptic ulcer at that time. The 111 patients whose ulcers did not

heal sufficiently within 12 weeks of treatment were randomized either to immediate surgery or another 12 weeks of medical treatment.

This study was published as a special supplement to the journal *Gastroenterology.*[18] Dr. Morton Grossman summarized the complex and inconclusive results. Of those patients with unhealed ulcers randomized to further medical treatment, 42 percent healed completely in the second 12 weeks of therapy. However, there was a high rate of recurrence of the ulcers in the medically treated patients during the two-year observation period. Cancer was found in 3.9 percent (25) of the 638 patients, but the indicators for cancer were not clear-cut. Grossman concluded that, despite the tremendous effort and careful design of the study, its fundamental question, whether medical or surgical treatment is better for gastric ulcers that don't heal promptly, remained unanswered.[19]

Surgery for duodenal ulcer

A cooperative group of VA surgeons started tracking the results of different types of surgery for duodenal ulcer in 1956. They published their retrospective analysis as a monograph in 1963.[20] After reviewing their findings, they concluded in 1972 that a prospective randomized study was needed to establish the best type of surgical procedure for this disease.

For the prospective study, patients were selected who needed surgery for their ulcers. They were not randomized until the surgeon made sure, during their operation, that any of the four operations under study could be performed safely. At that point, a sealed envelope was opened in the operating room to identify the operation for the particular patient. In 17 VA Hospitals, 1,358 patients with duodenal ulcer requiring operation were randomly assigned to vagotomy and drainage, vagotomy and distal antrectomy, vagotomy and hemigastrectomy, or gastric resection alone.

The post-operative mortality and morbidity rates were least with vagotomy and drainage, but the incidence rate of recurrent ulcers during the two years after operation was highest with this procedure. The late sequelae tended to be more frequent and severe in relation to the amount of stomach removed. No statistically significant differences in the frequency of good and excellent results, as estimated by the surgeon, the patient or an independent physician, were found among the four surgical procedures.[21]

Esophageal varices

This very difficult clinical problem was studied by a group of surgeons for nearly twenty years (1956 through 1975) who attempted a randomized study comparing portacaval shunt surgery with non-surgical treatment. They studied patients who had known varices that had not yet bled and also patients who had already bled from their varices. They found that half of the medically treated patients would die from bleeding either from the varices or from other sources during the 3½-year follow-up period. While the operative mortality (13.5 percent) was not itself a primary factor in survival after a prophylactic shunt, there were serious complications. Liver failure and ulcer disease were the most serious threats to the shunted patient if the patient survived one year after surgery. An operation in the setting of established liver disease was still incompatible with a lengthened survival. They concluded that the portacaval shunt was not recommended in the nonbleeding, established cirrhotic patient with recent ascites, jaundice or encephalopathy.[22]

In the even more dismal context of the patient who has already had bleeding from his or her esophageal varices, 155 patients were randomized, 78 given non-surgical treatment and 77 receiving shunt surgery. They were followed for an average of 5½ years. Of the medically treated patients, 37 percent survived the observation period, as did 55 percent of the shunted patients. The group concluded that "irrespective of the frequency or degree of previous or recent hemorrhage from varices, and previous or recent hepatic failure, the stabilized cirrhotic patient has a more favorable opportunity for a prolonged survival if he receives a portacaval shunt. Age, varying values of standard liver function tests, histological changes in the liver, the threat of peptic ulcer, the ravages of hepatic failure and post-shunt encephalopathy affect but do not appear to significantly alter this outcome, especially when the alternative is a conservative approach to a threat of lethal rehemorrhage."[23]

In the discussion after this study was presented, Ronald A. Malt, M.D., of Harvard Medical School and the Boston VA Medical Center, commented, "The enormous amount of data in the complete manuscript, and the objectivity with which Dr. Jackson and his colleagues have analyzed it, sets a new standard in this area. And I am afraid that the rest of us who are interested in portal hypertension are going to have to work a lot harder just to try to keep up with it."

Coronary artery surgery studies

Angina pectoris and myocardial infarction, caused by obstruction of the coronary arteries, become increasingly important as a patient ages. Surgical attempts to improve coronary circulation came into common use in the 1960s, but no objective studies had been done by this time to prove whether the techniques actually helped patients.

In 1960, a group of VA surgeons designed a cooperative study to evaluate the Beck procedure, in which powder was introduced into the pericardial sac to cause adhesions between the pericardium and the heart. About 150 patients were randomized either to surgery or to non-surgical treatment. After following these patients for four years, the group concluded that the outcome of surgery was no better than that of medical treatment.[24]

Next, the group studied the Vineberg operation, a procedure in which the internal mammary artery was implanted into the ischemic myocardium, which at that time was the most widely used operation for coronary artery disease. A pilot study of the Vineberg procedure began in 1966 and was expanded to a full study in 1968. In all, 146 patients were enrolled. The long-term results showed no significant effect on survival after an average follow-up of 9.3 years.[25]

By 1970, coronary artery bypass surgery had come into frequent use, and the group began a pilot study of that procedure (Chapter 18).

Studies supported by the National Cancer Institute

Another important group of studies were conducted in collaboration with the National Cancer Institute (NCI). These included surgical adjuvant studies, studies of medical treatment for inoperable lung cancer, and studies of treatment for prostate cancer. We'll discuss each of these types of studies on the following pages.

Surgical adjuvant studies

Shortly after Lyndon Lee, M.D. (Figure 12.5), arrived in VA Central Office in 1957 as Surgery Service Research Coordinator, Dr. John Barnwell introduced him to NCI Director Rodney Heller. Heller placed Lee on one of his Advisory Groups, and together they negotiated a collaborative program[26] to study the effects of adjuvant treatments given patients at the time of their surgery for primary cancers. A group of interested VA surgeons was assembled and the Follow-up Agency agreed to provide statistical support.

Over the next 25 years, this group studied almost 12,000 patients undergoing primary surgery for cancers of the lung, pancreas, esophagus, stomach, colon and rectum.[28-27] As promising new treatments were identified, the group would decide whether to start a new protocol to test them. The statisticians from the Follow-up Agency would design the protocols for the trial, always with strict randomization: new treatment plus surgery compared with surgery alone. Possible dangers of the treatments were tracked carefully, and a protocol was discontinued if patients on the adjuvant treatment did not respond as well as the control group.

Some of the most important findings of this group turned out to be the negative results. Adjuvant chemotherapy did not improve the outcome of surgery for cancers of the stomach, pancreas, esophagus or lung, findings that since have been repeatedly confirmed. Similarly, despite its popularity at the time, preoperative radiation did not improve the outcome of surgery for lung cancer. These negative findings spared patients the danger, discomfort and cost of futile efforts to improve their chances of cure.

On the other hand, this group showed that preoperative radiation did improve the chance of cure in rectal cancer and that 5-fluorouracil adjuvant chemotherapy increased the numbers of disease-free patients as well as the overall survival of patients with colon cancer.[27]

Treatment of inoperable lung cancer

This cooperative study group, also supported by the NCI, systematically evaluated the effect of therapies on patients with inoperable pulmonary carcinoma. This series of carefully controlled clinical trials involving over 9,000 patients began in February 1958 and continued until 1975.

At first, the group used an inert compound as a control against the agent to be tested because no valid evidence was available that any form of therapy prolonged the survival of patients with inoperable lung cancer. After cyclophosphamide was found to have a slight effect in prolonging survival in patients with extensive disease, this medication became the standard against which other therapeutic modalities were compared. The group's first protocol showed that cortisone had a deleterious effect. In patients with disease limited to the thorax, they found that radiotherapy prolonged survival slightly. Cyclophosphamide and BCNU had similar effects, achieving a slight but statistically significant improvement in prognosis.

Taking into account histologic type, the research team found that nitrogen mustard has its greatest effect on patients with highly and moderately differentiated squamous cell lung cancer types, while

cyclophosphamide was more effective in patients with undifferentiated small cell type. This differential effect of alkylating agents had been suspected before but had rarely been demonstrated with solid tumors such as bronchogenic carcinoma.

In addition to its careful randomized treatment comparisons, this group kept meticulous clinical records and performed intensive histologic analysis of tumors. Their work improved the understanding of lung cancer pathology and identified patient characteristics that influence survival and response to treatment.[12]

Prostate cancer studies

This NCI-supported VA cooperative study group studied some 5,000 patients with prostate cancer between 1959 and 1975. Their early results conclusively showed that, while administration of stilbestrol in daily doses of 1.0 to 5.0 mg has a therapeutic effect on metastatic prostatic cancer, it causes cardiovascular complications. While these complications are dose-related, they disappear only when ineffective doses of stilbestrol are given. They also found bilateral orchiectomy to be of questionable value in any stage of prostatic carcinoma.

The study group concluded that, owing to the cardiovascular complications, treatment with estrogens should be withheld in prostatic carcinoma with regional spread until the development of symptoms severe enough to warrant the risk of cardiovascular complications. They also concluded that, in early focal prostatic cancer of elderly men, no treatment should be given, as these tumors are very slow-growing and the complications associated with surgical or hormonal treatment outweigh any possible benefit of treatment.

While additional advances have been made in prostate cancer treatment since these studies were completed, the finding of the adverse cardiovascular effect of high-dose stilbestrol had a profound effect on practice in the period following this study.

Outpatient psychiatry

Associated with the psychopharmacology group (Chapter 8) but separate from it was a cooperative group that worked in outpatient clinics in VA's freestanding Regional Offices. Coordinated by Maurice Lorr, Ph.D., of VA Central Office, this group conducted single-protocol studies intended to improve treatment of psychiatric outpatients. The studies took advantage of the rating scales that Dr. Lorr was developing, and led to the development of other rating scales.

In a 1960 study by this group, 23 VA mental hygiene clinics collaborated in a 12-week, double-blind study of meprobamate and chlorpromazine to learn whether individual psychotherapy with a tranquilizer would be more effective in reducing anxiety and hostility than psychotherapy alone or psychotherapy with either of two control substances. One hundred eighty patients were randomly assigned to five treatment groups. Comparative analysis after eight weeks of treatment revealed that neither chlorpromazine nor meprobamate used adjunctively had an advantage over psychotherapy alone, or over psychotherapy with either of two control substances, in reducing anxiety and hostility. Both patients and therapists agreed with this finding.

A 1962 study evaluated the short-term effects of a new tranquilizer, chlordiazepoxide, on the anxiety and tension of newly accepted patients. The four-week project using a double-blind design was conducted in 23 VA mental hygiene clinics on 150 male patients referred for psychiatric care. Each patient was randomly assigned to one of six treatment groups. The effects of treatment were evaluated by means of 10 initial and terminal tests and on the basis of weekly self-reports on an adjective rating scale. In addition, patients assigned to psychotherapy were evaluated before and after treatment by their therapists. Patients on the drug under study reported significant reduction in anxiety and increased vigor during the first week, but these effects disappeared by the study's close. However, psychotherapists reported that patients receiving the drug were significantly less severely ill and that their rapport with others improved. The prescribing physician also judged patients receiving the drug to be improved. On the other hand, all patients receiving a capsule, whether a placebo or an active drug, reported greater reduction in anxiety and depression and greater overall improvement than those not receiving a capsule.[28]

Comments on the cooperative studies of the 1960s

Most of the studies described here share features characteristic of VA cooperative studies of the 1960s, characteristics that decreased or disappeared in later years. In general, such studies were products of an ongoing coalition of investigators focused on a general clinical problem. When one study was completed, the group, which by that time had formulated new questions, often moved on to another related study. This blurred the boundaries between studies, in contrast to the crisply defined studies begun in the 1970s and later.

Many of these studies were coordinated and analyzed by contract statisticians, rather than by those within the VA. In some, protocol changes occurred by consensus rather than by decision of a formal review group. A large number of protocols were carried out, with continuity being provided by the group of physicians performing the studies rather than in the protocols themselves. A remarkable feature was the loyalty of the groups to their goals. Even the experience of one disappointment after another (as for the lung cancer treatment group) did not discourage them from seeking reliable ways to improve the outlook for their patients.

Obsolescence of a drug or procedure is a problem that remains important in deciding which of these very ambitious and expensive studies to undertake. If something better comes along, the study is no longer relevant. But if something better doesn't appear, learning whether the intervention will benefit the patient is an obvious step forward. Some cooperative studies begun in the 1960s were abandoned after a short period, either by the investigators themselves or by the Cooperative Studies Evaluation Committee, when it appeared that the promise of further benefits appeared limited.

References

1. Interview with Clifford Bachrach, M.D., May 7, 1992 at Dr. Bachrach's home in Gaithersburg, MD.

2. Interview with Lawrence W. Shaw, M.S., February 3, 1994 at Mr. Shaw's home in Florida.

3. Mimeographed document provided by Mr. Lawrence Shaw. "Highlights of the First Meeting of the Cooperative Studies Evaluation Committee." 1966.

4. Higgins, G., Shields, T. and Keehn, R., "The solitary pulmonary nodule: Ten-year follow-up of Veterans Administration-Armed Forces Cooperative Study." *Arch Surg*, 1975. **110**: 570-575.

5. Falk A and Fuchs, G.F., "Prophylaxis with isoniazid in inactive tuberculosis. A Veterans Administration Cooperative Study XII." *Chest*, 1978. **73**: 44-48.

6. Salkin, D. and Huppert, M. "Progress report of the Veterans Administration - Armed Forces Coccidioidomycosis Study Group, 1970." *Veterans Administration - Armed Forces Coccidioidomycosis Study Group*. San Francisco, CA: VA Hospital, San Fernando, 1970, **14**:

7. Telephone interview with John N. Galgiani, M.D., September 27, 2002.

8. Sutliff, W.D., "Histoplasmosis Cooperative Study V. Amphotericin B dosage for chronic pulmonary histoplasmosis." *Am Rev Resp Dis*, 1972. **105**: 60-67.

9. Busey, J.F., " Blastomycosis III. A comparative study of 2-hydrostilbamidine and amphotericin B therapy." *Am Rev Resp Dis*, 1972. **105**: 812-818.

10. *Medical Research in the Veterans Administration, FY 1966*. Washington, DC: Government Printing Office, 1966, 73-74.

11. *Medical Research in the Veterans Administration, FY 1969*. Washington, DC: Government Printing Office, 1969, 81.

12. *Medical Research in the Veterans Administration, FY 1974*. Washington, DC: Government Printing Office, 1974, 92-93.

13. Milliken, J.A., Pipberger, H., Pipberger, H.V., Araoye, M.A., Ari, R., Burggraf, G.W., Fletcher, R.D., Katz, R.J., Lopez, J., E.A., McCans, J.L. and Silver, A.M., "The impact of an ECG computer analysis program on the cardiologist's interpretation. A cooperative study." *J Electrocardiology*, 1983. **16**: 141-150.

14. Katz, H.M. and Bissel, G., "Blood sugar lowering effects of chlorpropamide and tolbutamide. A double blind cooperative study." *Diabetes*, 1965. **14**: 650-657.

15. Veterans Administration Cooperative study of Atherosclerosis Neurology Section, "An evaluation of anticoagulant therapy in the treatment of cerebrovascular disease." *Neurology*, 1961. **11**: 132-138.

16. Veterans Administration Cooperative study of Atherosclerosis Neurology Section, "Estrogenic therapy in men with ischemic cerebrovascular disease: effect on recurrent cerebral infarction and survival." *Stroke*, 1972. **3**: 427-433.

17. Veterans Administration Cooperative Study of Atherosclerosis Neurology Section, "The treatment of cerebrovascular disease with clofibrate." *Stroke*, 1973. **4**: 684-693.

18. Littman, A., "The Veterans Administration cooperative study on gastric ulcer." *Gastroenterology*, 1971. **61**: 567-640.

19. Grossman, M.J., "Resume and comment in The Veterans Administration cooperative study on gastric ulcer." *Gastroenterology*, 1971. **61**: 635-640.

20. Postlethwait, R.W., *Results of surgery for peptic ulcer; a cooperative study by twelve Veterans Administration hospitals.* Philadephia: W.B. Saunders Company, 1963

21. Price, W.E., Grizzle, J.E., Postlethwait, R.W., Johnson, W.D. and Grabicki, P., "Results of operation for duodenal ulcer." *Surg Gynec Obstet*, 1970. **131**: 233-244.

22. Jackson, F.C., Perrin, E.B., Smith, A.G., Dagradi, A.E. and Nadal, H.M., "A clinical investigation of the portacaval shunt: II. Survival analysis of the prophylactic operation." *Am J Surg*, 1968. **113**: 22-42.

23. Jackson, F.C., Perrin, E.B., Felix, W.R. and Smith, A.G., "A clinical investigation of the portacaval shunt: V. Survival analysis of the therapeutic operation." *Ann Surg*, 1971. **174**: 672-701.

24. *Medical Research in the Veterans Administration, FY 1968*. Washington, DC: Government Printing Office, 1968, 85.

25. Bhayana, J., Gage, A.A. and Takaro, T., "Long-term results of internal mammary implantation for coronary artery disease. A controlled trial by the participants of the Veterans Administration Coronary Bypass Surgery Cooperative Study Group." *Ann Thorac Surg*, 1980. **29**: 234-242.

26. Interview with Lyndon Lee, M.D., April 7, 1988 at a restaurant in Bethesda, MD.

27. Hrushesky, W.J.M., "The Department of Veterans Affairs' unique clinical cancer research effort." *Cancer*, 1994. **74**: 2701-2709.

28. *Medical Research in the Veterans Administration, FY 1962*. Washington, DC: Government Printing Office, 1962, 66.

Chapter 14. The Research Career Development Program

One of the major obstacles confronted by the VA medical research program in its early days after World War II was the shortage of clinicians with advanced training in research. Funds were available to support meritorious research, and by the mid-1950s the problems of inadequate space had begun to be addressed. Some of the very successful clinician-investigators who started their research in the 1950s—Roger Unger and Solomon Berson, for example—had no research training before they joined VA. But many of them were outstanding individuals with energy, stamina and intelligence, and the humility to learn from their colleagues and technicians and to persist beyond early mistakes. Many others who tried to enter research without the needed preparation soon became discouraged. Somehow, VA itself would have to find a way to attract and keep promising candidates if the research program was to grow and flourish.

The Clinical Investigator program

In 1956, Martin Cummings, M.D., Director of the Research Service, together with John Nunemaker, M.D., Director of the Education Service, supported by the new ACMD for Research and Education, John Barnwell, M.D., and the new Chief Medical Director, William Middleton, M.D., started a program to address the shortage of clinical researchers. Thus began what was to become the Research Career Development Program, which aimed to create an elite leadership corps of clinician-researchers within VA. They persuaded Marjorie Wilson, M.D., who had left Central Office in 1953 to complete her clinical training, to return to VA and start this program.[1] She reviewed similar programs then in existence and tried to incorporate their best features. The result was the Clinical Investigator program.

The VA FY 1957 annual report to Congress, *Medical Research in the Veterans Administration,* describes this new program:

> "Because of a national shortage of scientific manpower, the Veterans Administration undertook a program to train specially qualified and interested physicians in research methodology. Known as VA Clinical Investigators, 23 young physicians were selected for special training in disciplines of medical research with special reference to basic studies in problems of aging. These young scientists are nominated by the medical school Deans' Committees after a local competition. The nominees are screened in national competition by a central selection committee. Those who are accepted will receive up to 3 years' training in research under the guidance of a senior preceptor while at the same time sharing clinical work as a member of the staff of a VA hospital. A modest amount of money is provided for supplies, equipment, and technical assistance to their work. This new program has been favorably commented upon by leaders of academic medicine."[2]

Clinical Investigators were treated as an elite corps. Dr. Wilson, serving as their advisor, would visit them in their labs and help them with any administrative problems.

All Clinical Investigators were invited to attend the annual VA research meetings, while other investigators had to compete for places on the program. In conjunction with these meetings, they

held special meetings of their own. At first, these were informal; the Clinical Investigators would get together to discuss mutual concerns.[1] Later, these meetings became scientific sessions of increasing formality.

The Clinical Investigator program developed into a huge success. Academic medical centers competed to recruit its graduates to their faculties. Nevertheless, many Clinical Investigators elected to remain in VA. The FY 1960 annual report to Congress about the VA research program notes that "The original purpose of the program was realized in the assignment of 16 previous Clinical Investigators to regular full-time staff positions by July 1 of this year."[3]

During its formative period, the Clinical Investigator program, though funded from the research budget, was administered by Education Service and perceived primarily as a training program. It soon became apparent that the awardees were already serious researchers, and in June 1961 the *Research and Education Newsletter* announced that, "The latest in a series of changes places the responsibility for the Clinical Investigator program in Research Service instead of the Education Service."[4] Although the awardees were not the beginners originally envisioned for the program, the Clinical Investigator appointment was key to their entering independent research careers, and most of them did so.

The Senior Medical Investigator program

In 1959, the Senior Medical Investigator program was begun to provide a small nucleus of well-established, highly successful clinician-scientists to serve as role models for younger research physicians. Dr. Wilson also initiated this program, modeling it on similar programs run by NIH and private foundations.[1] The first two Senior Medical Investigators, Drs. Samuel Bassett and Edward Freis, were appointed in 1959. Senior Medical Investigators were expected to spend the majority of their time on research, while maintaining a clinical presence in the host hospital. They attended the annual research meetings with the Clinical Investigators and served as a critical audience for their research papers.

Table 14.1. Senior Medical Investigators

	Year appointed	Specialty
Edward Freis, M.D.	1959	Cardiology (Chapter 9)
Samuel Bassett, M.D.	1959	Nephrology
Ludwig Gross, M.D.	1960	Hematology – oncology
Oscar Auerbach, M.D.	1960	Pathology – pulmonary (Chapter 10)
Morton Grossman, M.D.	1962	Gastroenterology
Solomon Berson, M.D.	1963	Nuclear medicine – endocrinology (Chapter 11)
Jay Shurley, M.D.	1967	Psychiatry
Paul Heller, M.D.	1969	Hematology
Rosalyn Yalow, Ph.D.	1972	Nuclear medicine (Chapter 11)
Sidney Ingbar, M.D.	1973	Endocrinology
Andrew Schally, Ph.D.	1973	Endocrinology
William Oldendorf, M.D.	1978	Neurology
Roger Unger, M.D.	1979	Endocrinology
Leo Hollister, M.D.	1982	Psychopharmacology (Chapter 8)
George Sachs, M.D.	1984	Gastroenterology
Jeremiah Silbert, M.D.	1990	Endocrinology – aging

The accomplishments of individual Senior Medical Investigators (Table 14.1) made important contributions to medical science, and most continued in VA for the remainder of their careers. Five of them (Freis, Gross, Yalow, Schally, and Oldendorf) won Lasker Awards and Yalow and Schally each won a Nobel Prize.

In the early days of this program, appointing Senior Medical Investigators was a very personal affair. Sometimes, candidates did not even know they had been nominated until they were informed of the selection.[5, 6] Notification was by a personal phone call from Dr. Middleton or another high official in Central Office. Each Senior Medical Investigator reported directly to the Central Office and received the highest possible personnel classification in the system. Central Office negotiated directly about individual needs, including funds that would be directly earmarked for each program.

The Research Associate program

Even though the Clinical Investigator appointment had been intended as an entry-level position, successful applicants generally had some research experience already. In some subject areas it was especially difficult to gain enough experience to compete for these awards. A bridge was needed between the clinical training period and the Clinical Investigator appointment, an opportunity to gain enough research experience to demonstrate that a candidate was likely to become a successful researcher. The advocates for certain research areas were successful in establishing programs to meet the clinician-researcher shortages in their own areas—first among these areas, psychiatry and psychology.

In 1961, VA announced a new program to alleviate the shortage of psychiatrists adequately trained for research. Directed by Samuel Kaim, M.D., the Research Associate in Psychiatry program involved a one-year training period for psychiatrists in the techniques of laboratory and clinical experimentation, under the overall guidance of a preceptor. The first two Research Associates in Psychiatry were appointed in March 1962, and a third began his work in June 1962.[7]

At about the same time, a similar program of Psychology Research Associates was begun with four appointments under the direction of H. Elston Hooper, Ph.D.[8] This program of two-year appointments for psychologists wishing to become research psychologists was announced late in 1961. During its time as a separate program, 87 psychologists benefited from this training, described as "one of the most desirable postdoctoral experiences in the Nation."[9]

Shortly afterward, Research Associate openings were announced in other physician specialties in which a shortage of research talent was identified: pathology, physical medicine and rehabilitation, orthopedics, oral diseases and gastroenterology.[10] Advocates of additional specialty areas made cases for establishing the Research Associate in their specialties, and by 1968, it had become a two-year program available to all physician specialties. By the early 1970s, the Psychology Research Associate program had merged with the Physician Research Associate program, which was now open to all VA doctoral-level clinicians.

The Medical Investigator program

By 1968, many distinguished physician-scientists in VA were considered to be too experienced for the Clinical Investigator appointment but not yet at the level of seniority to qualify as Senior Medical Investigator. At that time, a new position was introduced in the Research Career Development Program, the Medical Investigator, an appointment intermediate between Clinical Investigator and Senior Medical Investigator. The first five appointments were made the following year. This position was described as one that "provides established, successful investigators an opportunity to pursue research activities for a major portion of their time (at the discretion of the investigator) with the remaining (time) spent in teaching and patient care. Candidates selected will be those for whom VA can anticipate continued productivity."[11] This new position was well-received, and 5, 7 and 13 appointments were made in 1969, 1970 and 1971, respectively.

With the Medical Investigator position in place, a "research career ladder" was now available to the career clinical scientist, though to move from one rung of the ladder to the next required approval of the review committee, and such approval was difficult to achieve.

In 1972, budgetary problems prompted a rethinking about the expensive Medical Investigator program. A senior-level salary plus substantial research support ($40,000 per year) went with the appointment. James Pittman, M.D., the ACMD/R&E at that time (Chapter 15), decided to place a moratorium on the program.[12] From 1973 through 1976, only eight appointments, including three reappointments, were made.

In 1975, Thomas Newcomb, M.D., ACMD/R&D (Chapter 15) and Marguerite T. Hays, M.D., Director, Medical Research Service (Chapter 16), decided to revive the Medical Investigator program under new guidelines, discarding the "ladder" concept. The new Medical Investigator position was a six-year appointment not immediately renewable. An awardee could apply for renewal only after serving a year as staff clinician at his/her medical center. In 1977 and 1978, five new appointments were made annually under the new guidelines. Appointment as Medical Investigator continued to be a rare honor throughout the program's existence.

Research and Education Trainee program

Even with the Research Associate program, there was still no "fellowship" level in the research career ladder. To fill this void, in 1968 Drs. Lionel Bernstein and Harold Schoolman, Directors of the Research and Education Services, established a fellowship program for young clinicians. Called Research and Education Trainees, these were physicians who had completed at least three years of postdoctoral clinical training. The traineeship allowed them to receive specialty training, including research experience. The research experience of these trainees was the responsibility of a "chief trainer" at the hospital, who selected the trainees and monitored their training experience. This program was funded by Research Service but administered by Education Service. A separate selection committee for each of 14 specialty areas reviewed applications from hospitals wanting to establish traineeship programs. This program grew over several years, and by the end of FY 1971, 67 Traineeship programs had been established in 35 VA hospitals. These traineeships were abruptly discontinued during FY 1972, reportedly due to a decision by the Office of Management and Budget to terminate such programs, including those at the NIH as well as VA. Fortunately, the VA residency program was large enough to absorb the trainees into specialty residencies, and incumbent trainees were able to complete their programs.

The Associate Investigator program

By the middle of the 1970s, competition for Research Associate positions had grown so keen that the qualifications of successful candidates were at an extremely high level. Persons with substantial bibliographies and established success in research began to edge out those wishing to enter a research career who had not yet had the opportunity to do so. At the same time, the VA research traineeship program, intended to meet this need, had been disbanded. To provide an entry level in the Research Career Development Program, a new position, the Associate Investigator, was established in 1976. To assure that this position remained targeted to entry-level applicants, it came with certain restrictions. Awardees received a lower salary than they would have received as staff physicians, and they were not eligible for a bonus being paid to VA physicians. There was a limit on the amount of research training and experience that a candidate could have before applying. Despite these restrictions, large numbers of excellent candidates continued to apply for the few positions available.

Review process for Research Career Development Program applicants

At the time that the Clinical Investigator program was initiated in 1956, VA appointed a distinguished committee of outside academicians to review applications for appointment and recommend program policy (Appendix IIj). At first, this committee was called the Selection Committee for Clinical Investigators. In 1964, presumably because they also reviewed nominations for Senior Medical Investigator positions, the committee became the Selection Committee for Clinical and Senior Investigators. In 1971, in recognition of the increased complexity of the program it reviewed, it became the Research Career Development Committee. In the late 1970s, a few VA scientists were added to the committee to present the intramural viewpoint, but the committee continued to be largely an outside group.

From the beginning, this committee concerned itself primarily with assuring that awardees' research experience was the best possible for both the awardee and VA.

Compensation of Research Career Development awardees

Initially, Clinical Investigators and Research Associates received lower salaries than they would have earned as full-time staff clinicians. In 1961, the Clinical Investigator earned $9,000 per year.[5] The July-August, 1966 *Newsletter* contains the information that Research Associates were ordinarily staffed at Full Grade, Step 1, though in some cases they were given Intermediate Grade. Clinical Investigators entered at Intermediate Grade, Step 3, if board eligible, or Step 6 if board certified.[15] At the same time, clinicians were being recruited one or two grades higher. This discrepancy in salary was apparently causing enough concern that it remained under review, with consideration given to making appointments at a grade level equal to those of staff physicians. Within the next several years, this transition was made, and subsequently these appointees received the same VA base salary as did their full-time clinician counterparts.

However, in 1975, when VA physicians began to receive a salary bonus, Career Development awardees (except Senior Medical Investigators) were denied the bonus, as there was no

demonstrable shortage of candidates for the appointments. This led to turmoil in the program, with some appointees moving into patient-care positions, others accepting the lower salary, and others receiving salary compensation from their affiliated universities to make up the difference. Despite this problem, the program continued to be vigorous. The number of highly motivated, well-qualified candidates always exceeded the number of vacancies to be filled. During the 1980s, the administration of the physician's bonus was liberalized to permit some bonus salary for Research Associates and Clinical Investigators, and the full bonus for Medical Investigators as well as Senior Medical Investigators.

Administration of the Career Development Program

After initiating the Clinical Investigator program, Dr. Marjorie Wilson administered it from her position in Education Service until she left Central Office in 1960. The first Senior Medical Investigators were appointed during her tenure, and she set up the review committee and established guidelines. After she left, the program administration shifted to Research Service. Dr. Harold Schnaper became coordinator for Internal Medicine awardees, and Dr. Lyndon E. Lee, Jr., for Surgery awardees. Later in the 1960s, as Program Chiefs were recruited to Central Office in the various clinical and research specialties (Chapter 12), the Program Chiefs became the primary Central Office contacts for the Career Development appointees in their particular fields. In 1965, Dr. Eli Nadel assumed responsibility for overall coordination of the program.

In 1968, the Directors of the Research and Education Services, Drs. Lionel Bernstein and Harold Schoolman, formalized their concept of a research career ladder for clinicians, starting with the traineeship and culminating in the Senior Medical Investigator appointments. In recognition of the importance of this program, a formal Career Development Section was established within Research Service, which also had responsibility for the Traineeship program of Education Service. Chester W. DeLong, Ph.D., was its Chief. In 1971, this Section became a part of a new Career Development and Program Review Division in Research Service under Dr. DeLong.

Figure 14.1. Chester W. DeLong, Ph.D.

In 1972, Ms. Darlene Whorley became Chief of the Career Development Section within that Division, and in 1973 Career Development again became a separate division in the new Medical Research Service, with Ms. Whorley continuing as its Chief.

Figure 14.2. Darlene Whorley

Figure 14.3. David Thomas

In 1978, when Ms. Whorley left Central Office for the San Diego VA Medical Center, Mr. David Thomas became Chief, Career Development Section, a position he held until 1990.

Follow-up of Research Career Development appointees

From the beginning of the Research Career Development Program, VA was concerned with determining whether the initial goal of enhancing VA's cadre of expert clinician-researchers had been met. The agency wanted to know if it was contributing its share to the nation's medical research manpower. To answer these questions on a continuing basis, careful records were kept of all appointees to the program, with a systematic follow-up every few years. Retention in VA or in a university position was considered a measure of success. From the beginning, retention was impressive. While some attrition occurred as time went on, many graduates spent their entire careers in VA.

In 1968, the current status of the 187 persons who had completed the Clinical Investigator program was listed in VA's Annual Report to the Congress. Of the 182 former Clinical Investigators still alive and located, 68 were currently in VA and five were in other federal institutions (40 percent in federal employment). Sixty-six (36 percent) were in universities or private research institutes. Eight (4 percent) were receiving further training and 35 (19 percent) were employed in primarily non-research situations. [16] Compared with outcomes for similar programs providing research experience for junior clinician-researchers, this was considered to be an excellent result.

A more recent systematic follow-up of Career Development Program awardees was carried out in 1990. At that time, 1,781 of the 1,858 persons who were or had been in the program were located. Many of them had been appointed at more than one appointment level. They included 16 present or former Senior Medical Investigators, 70 Medical Investigators, 548 Clinical Investigators, 1,016 Research Associates and 428 Associate Investigators. Of the 1,742 living, non-retired appointees

located, 834 remained in VA, yielding an overall retention of 48 percent. Another 369 (21 percent) were in universities. Seventeen (1 percent) were in governmental positions other than VA, including the NIH. Sixteen (1 percent) were in industry, and 506 (29 percent) were in private practice. Altogether, of those still active professionally, 70 percent held government or academic positions.

Looking more closely at the 1,212 former Career Development appointees who had been in the program prior to 1981, 1,143 were located. Thirteen were retired and 24 had died. Of the remaining 1106, 401 (36 percent) were still in VA and 14 (1 percent) were in other government service. Two hundred seventy-six (25 percent) were at universities, 13 (1 percent) were in industry and 402 (36 percent) were in private practice.[17]

Hence, 10 to 34 years after they began their assignments in the Career Development Program, 62 percent of Career Development Program awardees who were still active professionally were in government or academic positions. The program had not only achieved its original goals, it had done so to a remarkable degree. Of those who remained in VA, many had become leaders, holding such titles as Associate Chief of Staff/Research (19), VA Service Chief (45), Chief of Staff (6), and many clinical section chiefs.

References

1. Interview with Marjorie Wilson, M.D., April 29, 1988 at Dr. Wilson's office in Washington, DC.

2. *Medical Research in the Veterans Administration, FY 1957*. Washington, DC: Government Printing Office, 4.

3. *Medical Research in the Veterans Administration, FY 1960*. Washington, DC: Government Printing Office, 25.

4. *R&E Newsletter*, June 1961. 15.

5. Interview with Paul Heller, M.D., March 3, 1993 at Dr. Heller's office at the Chicago Westside VA Medical Center.

6. Interview with Oscar Auerbach, M.D., October 30, 1992 at Dr. Auerbach's office at the East Orange, NJ VAMC.

7. *R&E Newsletter*, May, 1962. 19.

8. *R&E Newsletter*, November, 1962. 14.

9. *Medical Research in the Veterans Administration FY 1968*. Washington, DC: Government Printing Office, 16-17.

10. *Medical Research in the Veterans Administration FY 1967*. Washington, DC: Government Printing Office, 53.

11. *Medical Research in the Veterans Administration FY 1969*. Washington, DC: Government Printing Office, 14.

12. Interview with James Pittman, M.D., February 27, 1992 at Dr. Pittman's office at the University of Alabama.

13. *R&E Newsletter*, July 1962. 8-9.

14. *R&E Newsletter*, January 1966. 2-3.

15. *R&E Newsletter*, July-August 1966. 4.

16. *Medical Research in the Veterans Administration, FY 1968*. Washington, DC: Government Printing Office, 15.

17. Thomas, D. *Review of Career Development Graduates.* Medical Research Service, 1990.

(Intentionally Blank)

Section V. Maturation
1968-1980

(Intentionally Blank)

Chapter 15. Transition Years, 1968–1973

The late 1960s and the 1970s saw the maturation of the VA Medical Research Service and the beginnings of today's Health Services Research and Development Service and Rehabilitation Research and Development Service.

Medical Research experienced a rocky and controversial transition, from a program personally governed by managers with close familiarity with the investigators and their projects, to one based on peer review and objective criteria. Until about 1968, funding of projects in VA was based on results of previous work. Budget was not a serious problem; money was available for programs that the experts in Central Office considered worth supporting. Even correcting for inflation, the budget was increasing enough to accommodate new programs without jeopardizing existing ones. Continuation of productive programs was encouraged.

In 1968, new leaders committed to excellence in science introduced a program of peer review modeled after that of the NIH. Individual research programs received grant-type reviews. This system, imposed on an intramural program that had been relatively stable, led to turmoil and dramatic policy reversals. Over the next decade, the VA Medical Research Program gradually transformed itself into the peer review-driven program that exists today.

New leadership in the Research and Education Office

In 1966, Lionel Bernstein, M.D., Ph.D., a gastroenterologist who had been Associate Chief of Staff for Research and Education at the Hines VA Hospital in Chicago and then Chief of Medicine at the Chicago West Side VA, joined Central Office as Director, Research Service. At about the same time, Harold (Hack) Schoolman, M.D., who had been Chief of the VA Midwest Research Support Center at Hines, became Director, Education Service.

Figure 15.1. Lionel Bernstein, M.D., Ph.D.

Figure 15.2. Harold Schoolman, M.D

Bernstein and Schoolman were good friends and considered themselves a team. For a time, each served as the other's Deputy. They were well acquainted with Lucien Guze, M.D., the influential Chief of Staff for Research and Education at the Wadsworth VA Hospital in Los Angeles. Bernstein and Schoolman were hired into their VA Central Office (VACO)

positions by Dr. Ben Wells, but both believed Guze played a key role in their recruitment.[1, 2]

In late 1968, Thomas Chalmers, M.D., came to Central Office as Assistant Chief Medical Director for Research and Education(ACMD/R&E.) Bernstein and Schoolman had actively recruited Chalmers and enlisted Chief Medical Director H. Martin Engle to help bring him to their team. Chalmers had been serving on the Cooperative Studies Evaluation Committee.[3] Together with Bernstein and Schoolman, he was dedicated to assuring high quality in the research program.

Figure 15.3. Thomas Chalmers, M.D.

End of the annual research conferences

VA's annual research conferences were becoming very large and costly in terms of both money and effort. Bernstein and Schoolman believed that the investigators would be better served by using the money to send them to meetings in their own specialties. After 1967, Research Service (later Medical Research Service) held only conferences for research administrators and advisors. Discontinuing the annual meetings meant that another setting was needed for presenting the agency's Middleton Award. A suitable event in the recipient's hometown was selected for the 1968, 1969 and 1970 awards. Dr. Middleton himself presented the 1971 and 1972 awards, at an Atlantic City, N.J., meeting of VA research administrators[4] and at the American Federation for Clinical Research; and for the 1973 award, a ceremony was held in VA Central Office, where the Administrator and Chief Medical Director did the honors.

The Middleton Awardees, 1968-1973

The 1968 Middleton Award went to Thomas Starzl, M.D., Ph.D., of the Denver VA Hospital, for his pioneering surgical transplantation of kidneys and other human organs, including the development of anti-lymphocyte serum and globulin to suppress rejection of transplanted organs. Starzl later accomplished the world's first successful liver transplant.

Figure 15.4. Thomas Starzl, M.D., Ph.D.

Roger Unger, M.D., (Chapter 7) received the 1969 award "for his conception of the physiology of metabolism of fats and carbohydrates, to better therapy for diabetes patients."

Andrew V. Schally, Ph.D., who later received the Lasker Award and Nobel Prize for the isolation and synthesis of hypothalamic hormones, won the 1970 Middleton Award "for his investigations of the physiology and biochemistry of hypothalamic neurohormones."

Figure 15.5. Andrew S. Schally, Ph.D., receiving the Middleton Award from Emmanuel Bresler, M.D., Associate Chief of Staff for Research and Education, New Orleans VA Medical Center

In, 1971, Marcus Rothschild, M.D., was honored "for basic and clinical research on the pathological biochemistry of the liver in alcoholism and other types of liver disease."

Figure 15.6. Marcus Rothschild, M.D., receiving the Middleton Award from Dr. Middleton

The 1972 Middleton Award went to Kenneth Sterling, M.D., for his important work with radioactive tracers. He was cited for developing the ^{51}Cr labeling of erythrocytes for *in vivo* study as a clinical tool, using labeled human serum albumin to determine albumin turnover rate and for his use of radioactive thyroid hormones to study the disposal and turnover of thyroxine and triiodothyronone in humans.

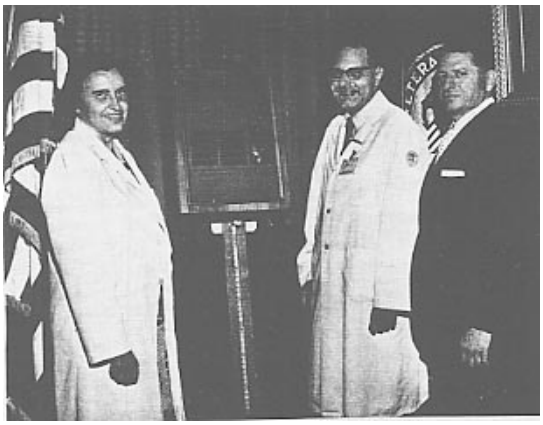


Figure 15.7. Kenneth Sterling, M.D. (center), standing by the Middleton Award with Rosalyn Yalow, Ph.D. (Chapter 11) and Bronx VA Medical Center Director Harold Jaffrey

Ludwig Gross, M.D. (Chapter 3) received the 1973 award "for demonstrating viral etiology of leukemia in mammals."

Figure 15.8. Ludwig Gross, M.D., and Thomas Newcomb, M.D., by the Middleton plaque

New approach to allocating research funds

Before the late 1960s, Central Office officials ran the research program in a very personal way, making most of the decisions about how much research money each hospital would receive.

In the earliest days of the post-World War II VA research program, the Committee on Veterans' Medical Programs (CVMP) (Chapter 4) had reviewed requests for individual VA research projects along with requests for research contracts from medical schools. These projects received peer review by the advisory committees of the National Research Council. At the same time (Chapter 3), "research laboratories" were being established at VA hospitals, each with a Chief, equipment, laboratory space and employees. From the late 1940s on, these "laboratories" were under the jurisdiction of a hospital Research and Education (R&E) Committee. As these laboratories recruited capable researchers, they grew and expanded into hospital-based intramural research programs, still under the jurisdiction of a local R&E Committee. The laboratory chief, first called the Assistant Director of Professional Services for Research (ADPSR) and later the Associate Chief of Staff for Research and Education (ACOS/R&E), was the Secretary of the R&E Committee. In the late 1940s and early 1950s, the funding for a hospital's research "laboratory" was in a stable, annualized budget. When new money was needed, the investigator submitted a request to Central Office through the R&E Committee and hospital management. The request was generally reviewed by the CVMP. If the CVMP recommended funding, Central Office would send the additional money to the hospital.

This mechanism, considered to be unduly complicated, was discontinued in late 1952.[5] After that, the R&E Committee at a VA hospital approved and recommended to Central Office, through the hospital manager, that additional research funds be made available to the hospital in a specified amount—for a specified purpose. Nevertheless, an attempt was made to provide each VA hospital engaging in research a definite annual research budget that it could count on.

By April 1954, the CVMP recognized that VA had changed its research focus from extramural to intramural. Contractual research was being phased down. The Committee questioned the value of the National Research Council (NRC) concerning itself with the VA intramural program, although

there was a feeling that government-funded research should have a disinterested civilian group checking work quality and direction. At the time, Dr. George Marshall Lyon, VA ACMD/R&E, explained that money was allotted to intramural programs according to such factors as:

1. Institution size or site
2. Quality of proposed work
3. Available patients
4. Degree of emphasis on particular fields
5. Local capabilities

Dr. Lyon felt that help was needed at the policy level, but he did not invite review of individual research projects.[6]

The first NRC survey of the VA Medical Research Program (Chapter 7), in 1960, describes it as highly decentralized, with four expert committees to advise the Chief Medical Director on national-level medical research policy and programming. In the survey, the NRC recommended that "the staff of the Research Service in the Veterans Administration's Central Office should be strengthened by the addition of three or four persons who are highly skilled in research methods and research administration."

At the local level, scientific review by the Research and Education Committee and/or the Deans Committee was an option. Records from the 1950s at one hospital, Palo Alto (Calif.), document R&E Committee review of investigators' written and oral presentations in defense of requests for support. But the review process was variable and undoubtedly was less complete at some hospitals. The hospital's annual requests to Central Office were generally based on historic funding plus additions for proposed recruitments. Since the overall research budget was increasing during those years, money was available to support most worthwhile recruitments, and there was no compelling impetus to phase out less-productive programs.

During the 1960s, VACO Research Service responded to the NAS recommendations and other pressures by boosting the scientific expertise in VA Central Office. Program Chiefs in various disciplines were appointed (Chapter 12). At the beginning of each fiscal year, the Director, Research Service, would allocate money to each of the Program Chiefs. They could use this money to recruit new investigators in their field and supplement the budgets of promising projects. Typically, the Program Chiefs traveled extensively, visiting individual investigators and potential recruits at the hospitals. When they were convinced that a new program was meritorious, they would provide funding for it, which would later be annualized into the hospital's research budget. The Program Chiefs participated actively in annual meetings, both for VA-wide research and in their particular disciplines. In some cases, they arranged meetings of VA investigators at national specialty research meetings to discuss mutual concerns, especially policy matters.

Some Program Chiefs established expert advisory committees in their disciplines to give general advice about research administration and some scientific review (Appendix IIg). This concept was focused and strengthened in 1965 when Drs. Marc J. Musser and Edward Dunner established 10 Research Evaluation Committees, each under the leadership of a Program Chief from Central Office. These Committees (Appendix IIh) generally reviewed investigators' progress reports, as

well as brief protocols for future research. Their advice helped the Program Chiefs to allocate funds and the hospital R&E Committee to distribute the research money received at the hospital.

A second NRC report, released in 1968, noted that: "The Central Office has appointed in the last two years a number of evaluation committees that, in the near future, will examine all research supported by the Central Office." It was recommended that VA enhance the role of its Research Evaluation Committees and, as appropriate, seek the advice of other outstanding peer-review groups to assure itself that its individual research projects were worthy of support.[7]

Funding considerations in 1967

By 1967, many knowledgeable observers felt that a change was needed for evaluation of VA research projects. At the NIH and elsewhere, a system of peer-review-based project funding was well established, and many felt that VA should undertake a similar type of program.

This opinion was by no means universal. VA research was intramural, carried out by VA staff in VA hospitals. In this sense, it was similar to the NIH intramural program: At NIH, considerable scientific review existed within and across institutes, but NIH intramural research was not subject to a grant-type review. Some excellent work was being done in VA under the existing system. VA researchers flourished in an environment where they could count on consistent support for their research, even when they ventured into new, perhaps risky areas or followed up on ideas not hammered out in the peer review system.

The hospital-based research programs often were still conceptualized as large "laboratories," each with the ACOS/R&E serving as its Chief. Some ACOSs had built up huge and flourishing research programs at their hospitals. These were flourishing under what was, usually, a benign dictatorship. New and continuing support of an investigator's projects was the prerogative of the R&E Committee, whose Secretary was the ACOS. In most cases, a simple memo or brief protocol was all that was required to justify funding a project. Newly hired staff members who entered the VA research program found it easy to get started. When new money was needed to set them up, a simple request to the Program Chief or Director of Research in Central Office usually sufficed.

On the other hand, it was difficult to control the way research money was spent. While some exchange with clinical services, such as clinical use of research facilities or research use of clinical facilities, was to be expected, some research projects seemed to have stopped advancing knowledge. The rapid growth of the research budget during the late 1950s and early 1960s showed signs of stabilizing, while the roster of qualified and motivated investigators grew. Money needed to be redistributed from unproductive programs to more promising ones. These concerns led to establishment of a revolutionary concept, the "Part 1-Part 2" system.

Part 1-Part 2 system

In 1967, Dr. Lionel Bernstein introduced a new "Part 1-Part 2" plan forVA research budgetary administration.

Under this plan, Central Office "Part 1" funds were awarded to a hospital specifically for a VA investigator's project. The amount of support was based on the advice of one of the Research Evaluation Committees. With a 20 percent allowance for local adjustments, these funds were earmarked for the specific research project. The plan was eventually to dispense about half of VA Research funds in this manner.[2]

"Part 2" funds, on the other hand, were to be distributed as institutional allocations, partially following the historical model in place prior to that time. These funds continued to be dispensed locally on the advice of the local hospital R&E Committee. However, redistribution of Part 2 funds between VA hospitals was to be based on an institutional site visit. This review would determine how well Part 2 funds were used for recruiting new personnel, starting research programs and establishing common facilities, and how well it all combined to help the patient care program,

To implement this Part 1-Part 2 concept, Lionel Bernstein established a Program Evaluation Section within Research Service and in late 1967 recruited Leon Bernstein, Ph.D. (no relation), from the Program Projects Grant Division of the National Heart Institute to be its Chief. Leon Bernstein, who had been a professor of physiology at the University College Hospital in London, had come to the Baltimore VA Hospital, where he was Acting ACOS/R&E—"acting" because he was not yet a U.S. citizen. He then moved to San Francisco, where he ran a laboratory at the VA hospital there and was briefly ACOS/R&E. From San Francisco, he moved to NIH but left there only a year later when Lionel Bernstein recruited him.[8]

Figure 15.9. Leon Bernstein, Ph.D.

Part 2 program

With a system for evaluation of individual projects by the Research Evaluation Committees already in place, Leon Bernstein's first effort was to establish a system to review institution-wide programs of individual VA hospitals, those to be funded by Part 2 money. Two large central committees (Appendix IIk) were established to oversee the Part 2 program reviews. Members of these committees served on audit teams that were to visit each hospital. In

composing the team for a given hospital, the Central Office staff tried to assure that it included representatives of all major areas of research at that hospital. The plan was that these committees would visit hospitals on a three-year rotation basis, interviewing each hospital's Research and Education Committee and all of its funded investigators. After this visit, the committee would recommend an amount for the Part 2 funding for that hospital for the next three years. This review was directed entirely at how well the hospitals were spending their "Part 2" monies, the undesignated general support research money they were receiving. Emphasis was placed on both the quality of research supported and the role of research in improving patient care. Projects that had passed "Part 1" review were exempted from Part 2 review.

Plans and implementation did not always match. For example, in advance of the Part 2 group's visit to Buffalo (N.Y.) in 1970, the ACOS/R&E received a long, complex form to be completed. He instructed the research investigators to write brief project summaries, about one page per project. The investigators did not understand that this site visit was going to determine their future —they had become accustomed to the system of Central Office Program Chiefs' visits, which generally resulted in more funds for a specific program and did not threaten other parts of the program.

The site visitors, led by Leon Bernstein himself, spent two days at Buffalo, interviewing all the investigators and meeting with the R&E Committee and top hospital administration. They toured the research space and asked penetrating questions. When the site visit report ultimately arrived at Buffalo, it analyzed all elements of the program with specific funding recommendations for each project, the total amounting to Buffalo's entire Part 2 budget for the next three years. The casually assembled one-page summaries, together with a short interview between the investigator and the visitors, resulted in specific funding decisions.

As the first round of Part 2 reviews progressed, a number of hospitals that had managed to build up large programs during the past 10 years were visited. In several, the emphasis on building up common resources had led to large amounts of money being placed under the control of the ACOS/R&E. As one ACOS/R&E expressed it, the site visitors "admired my extensive common resources very much, and then cut the budget."[9] A number of very vocal ACOS/R&Es complained vigorously about the Part 2 program. Lionel Bernstein, the Director, supported Leon Bernstein and refused to make any alterations in the committees' decisions. Failing to find a sympathetic ear in the Research Office, the complainers went to higher officials in Central Office. Soon, Central Office was full of polarized opinions for and against the Part 2 program.

Part 1 reviews

Once Part 2 program visits were well underway, Leon Bernstein turned his attention to reviewing individual research projects. The old Program Evaluation Committees were disbanded. One round of reviews was skipped to allow a "settling down."[8] Then a new group of Research Evaluation Committees (Appendix IIh) began to review projects.[10, 11] Applicants received elaborate, complex instructions on how to present their projects. When instructions were not properly carried out, the projects were returned to the investigator without review. At the same time, these new committees received clear mission instructions to be much less

permissive than the old Program Evaluation Committees. For the first time, major emphasis was on the prospective research plan as well as evaluation of the investigator's research accomplishments. Scientists who had been accustomed to a cursory review of their research plan, resulting in continuation and expansion of their funding, suddenly found their projects being disapproved. Again, protests arose from the field. But leadership in Research Service stood firmly behind its new peer review system, followed by people complaining elsewhere in Central Office. The division of opinions within Central Office became even more pronounced. Officials responsible for patient care services worried that these changes in research policy were hurting important clinicians at the hospitals.

Downfall of the Part 1-Part 2 program

Lionel Bernstein, Schoolman and Chalmers had sought to use a much scaled-down version of the NIH national grants peer-review methodology within the context of a nation-wide intramural system of 170 VA hospitals. Their aim was to support high-quality research while enhancing the effect of research on VA patient care and on medical schools affiliated with VA hospitals. Many observers applauded their goals. But by late 1969 and early 1970, the Part 1-Part 2 system was generating protests. Many considered the review process too rigid. Some of the most powerful ACOS/R&Es found their power bases eroding and objected strenuously.[12, 13] The resulting controversy in Central Office eventually led to abrupt policy and leadership changes in the Research and Education Office and in Research Service.

Leadership changes

In January 1970, Mark (Jim) Musser, M.D., who had previously been Director, Research Service, and ACMD/R&E, became VA's Chief Medical Director (CMD). He recruited Benjamin Wells, M.D., also a former ACMD/R&E, to return to Central Office as his Deputy. Musser and Wells had been keeping in touch with Research Service while they were at the Regional Medical Programs. They were concerned about the dissatisfaction in the field stirred up by the new Part 1-Part 2 program. They did not object to the peer review principle; indeed, the Program Evaluation Committees had started during their research leaderships. However, they were troubled by the rigidity of the present program and the abruptness of changes it imposed on the field.[14]

On his first day as CMD, Musser met with Thomas Chalmers (the ACMD/R&E) and told him there were to be major changes in running the research program. Chalmers contacted NIH the same day, and accepted an appointment they had offered him earlier.[3] A short time later, Lionel Bernstein and Harold Schoolman received memos to the effect that they were to be reassigned from their present positions. During the next month or so, Lionel Bernstein reviewed VA needs in Health Services Research and Development and wrote a prospectus for this program (Chapter 17). He then moved to the Department of Health, Education and Welfare. A few months later, Leon Bernstein was reassigned from his position as Chief, Program Evaluation Section, to head up a Health Services Research and Development program.[15]

Musser appointed Lyndon Lee, M.D., his old Deputy from Research Service, to be the new

ACMD/R&E. Lee held that position for about a year, until he became ACMD for Professional Services in February 1971. Lee was as unhappy as Musser about the way the Part 1-Part 2 program was being administered. Lee appointed as his deputy Laurence Foye, M.D., who had been Director of Education Service, and Foye then served as Acting ACMD/R&E during the 1971 interim between the terms of Lee and his successor, James Pittman, M.D. During the interim, until John Bailer, M.D., was recruited as Director of Research Service at the end of 1970, James Matthews, M.D., and Abraham Dury, Ph.D., "held the Research Program together."[13] Basic institutional research support of the Medical Centers was held more or less constant, with adjustments upward after successful Part 1 reviews but no response to unsuccessful reviews. After Leon Bernstein left Research Service, Chester DeLong, Ph.D., assumed responsibility for Program Review while continuing to run the Career Development Program. He recruited Mr. Gerald Libman to be responsible for Program Review and Ms. Darlene Whorley for Career Development.

Under DeLong, the same basic system of Part 1 review was continued. The major difference was in its implementation. Minor irregularities in the applications were permitted, and deadlines were stretched in hardship cases. Also, an adverse Part 1 review did not result in a decrease in a hospital's research budget. Only a recommendation for start-up of a new Part 1 program or an increased support of an ongoing one affected the hospital's budget.[16]

"Total Institutional Review"

Lyndon Lee recruited John Bailar, M.D., from the National Cancer Institute to be Director of Research Service. Bailar had worked with VA on the NCI-funded VA urology cooperative studies, including the important study of the use of stilbestrol in prostate cancer that showed a 5mg/day dose to cause cardiovascular morbidity.[17, 18] Lee hoped that Bailar, who had a strong background in epidemiology, would help makeVA a giant in this area.[15]

Working with DeLong, Bailar started a program of "Total Institutional Review." Under this program, the entire hospital research budget would be determined by a site visit made to the hospital every three years. In their budgetary recommendations, site visitors were to take into account currently approved Part 1 programs, existing common resources left from the Part 2 program, and a projection of the hospital's needs over the next three years as determined at the site visit and in consultation with representatives from the affiliated medical school. The Part 1 funds were merged into this total hospital research budget, and new funding was not to be expected until the next site visit. The Regional Coordinators organized and staffed these site visits. The visiting teams were made up of VA investigators and ACOS/R&Es, as well as deans and other leaders from affiliated medical schools. These were full-dress affairs, not much different from the old Part 2 visits, except that the visitors now took into account the hospital's Part 1 experience. In addition, they attempted to sort through the optimistic input from the hospitals and medical schools to arrive at a realistic projection of expected growth over the ensuing three years.

At the initiation of this institutional review program, the Part 1-Part 2 system, which had been "on hold," was terminated. Hospital budgets were frozen at the level where they stood and remained essentially stable until the institutional site visit under the new system. Centralized

Part 1 review was discontinued and the hospital Research and Education Committees were expected to undertake peer review of their own research applications.[19]

At the time this new program began and when the totally decentralized budgets had been allocated, there was inadequate funding to include all of the recently approved Part 1 programs. These were funded at only 30 percent of approved levels, causing considerable hardship for "growing" programs. They had recently succeeded in recruiting "stars," new investigators whose programs were reviewed at that time. As a result, during the next several years of total decentralization, growing programs found it hard to make ends meet.

The institutional site visits continued with few problems until the visit to one of the largest research programs in the country. On that particular site visit, after a key visitor had to drop out at the last minute, enough controversy about the process arose that Dr. Musser decided to place a moratorium on that program as well.[20-22]

With review of institutional and individual projects on hold, the responsibility of the ACOS/R&E and the R&E Committee at the hospital was now more clearly defined than before. The R&E Committees were expected to undertake their own peer review of programs and be accountable for the quality of research. Various systems were worked out, generally involving ad hoc reviews. Some groups of hospitals collaborated to review each other's projects or set up regional peer review. There was general displeasure with the situation, however.[23]

James A. Pittman, M.D., and Thomas F. Newcomb, M.D.

Dr. James Pittman came to Washington from Birmingham, Ala., to become ACMD/R&E in mid-1971 and remained until 1973, when he returned to Birmingham as Dean of the University of Alabama Medical School. An endocrinologist and nuclear medicine physician, since 1956 Pittman had been Chief of Nuclear Medicine at the Birmingham VA Hospital, as well as at the University of Alabama at Birmingham. He was also a highly respected investigator in endocrinology. He recruited Lawrence Hobson, M.D., Ph.D., an expert in clinical pharmacology, to be his Deputy.

Figure 15.10. James Pittman, M.D.

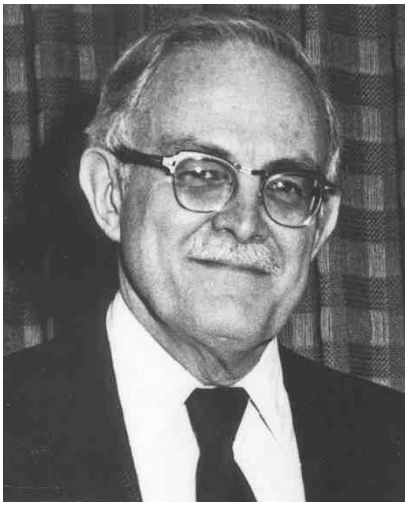


Figure 15.11. Lawrence Hobson, M.D., Ph.D.

A few months after Bailar returned to the National Cancer Institute, Pittman persuaded Thomas F. Newcomb, M.D., a hematologist and ACOS/R&E at the Gainesville (Fla.)VA Hospital, to come to Washington as Director, Research Service.[21]

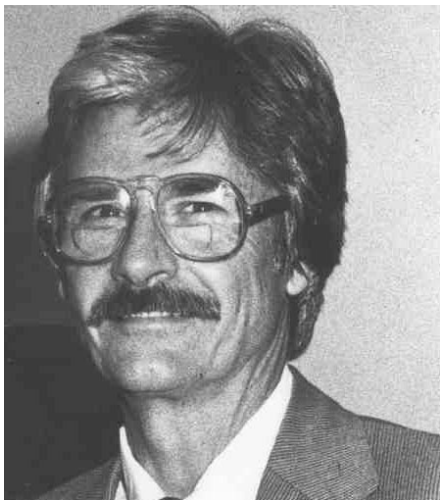


Figure 15.12. Thomas Newcomb, M.D.

Newcomb and Pittman re-establish peer review

Dr. Newcomb had been concerned about the problems he was encountering as ACOS/R&E at Gainesville stemming from the total decentralization of research funding. The R&E Committee was expected to use peer review in allocating their funds but was provided no guidance or help from Central Office in doing so. Newcomb had been trying to form a consortium of East Coast VA hospitals that would work together to substitute their own peer-review system for the absent Central Office peer-review mechanism. One of Newcomb's first

acts after arriving in Washington was to re-establish peer-review committees, now known as Merit Review Boards, to evaluate individual programs. Decisions of these committees were advisory to the hospital R&E Committees and at first did not directly affect funding.

Re-establishing these review committees was made more difficult by a new law requiring that all federal committees be chartered by the Office of Management and Budget (OMB). Newcomb worked with OMB to charter a new group of Merit Review Boards, but he also went ahead and set up individual peer review, even without a charter. For the first year or so, these Boards functioned ad hoc, without a charter. For one round of review, travel monies of the board members were denied. Deliberation was by conference call. However, in the beginning, Newcomb continued the system of decentralized total hospital funding with some adjustments in response to new merit reviews. It was not until 1974 that the new Merit Review Boards were actually chartered (Appendix II l).[23]

RRAGs and the RAC

Newcomb was bombarded with visitors who wanted him to help solve new problems at the hospitals, especially ones centered on meeting the needs of their new recruits. Other visitors described problems unanticipated by the institutional review group when their three-year budget was established. Some hospitals had not been visited before the moratorium and were still functioning with the same budgets they had in 1969. To address these diverse situations, Newcomb created a new advisory mechanism, the Regional Research Advisory Committees, or RRAGs, later called the RAGs.[23] As initially conceived, the RRAGs were four committees, one from each of the four geographic research regions, each charged with reviewing proposals from another region. At first, the RRAGs met simultaneously every two months in Central Office. Each RRAG was set up as a three-person committee, with three-year rotations, chaired by the member in his or her final year of RRAG service.

The first assignment to the RRAGs was to review a backlog of administrative requests that Newcomb had been deliberating. These were generally sketchily documented, and the RRAG groups often found it difficult to decide whether a proposal had scientific merit. A major concern was whether the requested funding would be beneficial for the hospital's patient care program. After a few meetings, the basic RRAG guideline was established that a proposal submitted for approval needed to meet a baseline of scientific merit as determined by an ad hoc review. If the proposal met this criterion, then the RRAG's decision would be based on the expected impact of the requested funding on the hospital.

Newcomb also formed an in-house Research Advisory Committee (RAC), which initially consisted of the four RRAG chairpersons, the Chair of the Cooperative Studies Evaluation Committee, and representatives from Professional Services, Health Services Research and Rehabilitation Research. This Committee met immediately after the RRAG meetings, reviewing the RRAG findings and making recommendations about them. It also discussed research policy and the needs of the research program.

Regional Coordinators

Even during the1960s, there were always vacancies in the roster of Program Chiefs; programs in those subject areas did not have a direct advocate in Central Office. As budgetary authority

moved away from the Program Chiefs, most of them left Central Office. Also, there was a need for an entity in Research Service to relate to the ACOS/R&E and through the ACOS to the hospital's research program as a whole. To meet this need, in 1969 Lionel Bernstein appointed five of the Program Chiefs to double as "Regional (Research) Coordinators." Later, the five regions were reduced to four, and, with attrition, the number of Regional Coordinators shrank. By 1974, two remained. Just as the Program Chiefs had been perceived by the field to have the real power during the early 1960s, the Regional Coordinators were now so perceived. The ACOS/R&E worked mostly with the Regional Coordinator and his or her assistant. They advised new ACOS/R&Es on their responsibilities and provided them with information on which hospitals would be useful examples of how a research program should be administered. They listened sympathetically to pleas and helped when they could.

Figure 15.13. Four of the five Regional Coordinators in 1968: Richard Filer, Ph.D., Elston Hooper, Ph.D., James Matthews, M.D., and Mark Walcott, M.D. (Howard Chauncey, Ph.D. not shown)

Program Specialists

By the time Newcomb came to Central Office, all of the Program Chiefs had departed. Drs. Abraham Dury, Gerald G. Hine, James Matthews, and Elston Hooper, who had been Program Chiefs, now had other responsibilities. Matthews was Newcomb's Deputy, and when Matthews left, Dury became the Deputy Director, Research Service. Hooper and Hine continued as Regional Coordinators but were now expected to cover the whole country. Research investigators in the field complained that they no longer had someone in Central Office who was both interested in and knowledgeable about their particular fields of scientific interest. Also, Central Office needed specialists in various research areas to carry on some of the former Program Chiefs' functions. To meet these needs, Newcomb established the position of Program Specialist.

Program Specialists were chosen from successful VA research investigators in the various subject areas. They were based at their field hospitals and spent only a minority of their time functioning as Program Specialists. Their function was to serve as liaison between individual investigators and VA Central Office. Initially, their major activities were as ombudsmen,

tasked with helping research investigators with problems. They also surveyed VA research in their fields and provided input for the annual report. Later, the Program Specialists were also asked to perform ad hoc scientific reviews of RRAG requests and suggest ad hoc scientific reviewers for Merit Reviews and Career Development applications.

The amount of work asked of the Program Specialists varied considerably from field to field. As partial compensation for this extra, unpaid work, the busier Program Specialists were given a secretary to help them. In time, new Program Specialists were nominated from the field on three-year rotations.

Basic scientists

Early in Newcomb's tenure as Director of Research Service, he faced turmoil among the basic scientists at several hospitals. Under the totally decentralized budgeting process, the R&E Committee had full responsibility for distribution of all institutional research funds and space. A few clinical leaders who did not accept the value of basic scientists to the hospital attempted to displace these scientists from their jobs and laboratories by pressuring the R&E Committees to remove them. Many of these displaced scientists were distinguished, academically acclaimed researchers who, not surprisingly, objected loudly and strongly. Newcomb sent Abraham Dury, previously the Program Chief for Basic Sciences, on site visits to meet with the scientists to try to resolve these problems. The R&E Committees' decisions were overruled, and the scientists were protected. As a result of these problems, Dury established an informal advisory group, including representatives from these and other medical centers, to present the viewpoint of the Ph.D. scientists.

Another outcome of Newcomb's tenure was the establishment of budgetary "Cost Center 104." During the 1960s, the Program Chiefs had protected the basic scientists. But with total decentralization, they needed other salary protection. Cost Center 104 was formed separately in the hospital research budget to pay the salaries of non-clinician principal investigators, and associated funds could not be used for other purposes. Dury later received VA's highest honor, the Exceptional Service Award, in part to recognize his work in stabilizing the role of the basic scientist within the research program.

Research Career Development Program

In 1969, Chester DeLong, Ph.D., was recruited from NIH to be Chief of the newly expanded Research Career Development Program (Chapter 14). His appointment was in Research Service, but he also reported to the Director of Education Service, as his responsibilities included the Research and Education Trainee program. De Long worked with the Career Development Committee to define the various rungs of the research career "ladder."

In early 1973, the OMB made the decision that research training programs were not in the best interests of the government. Along with NIH training grants, the VA Research and Education Trainee program was discontinued. In addition, Pittman and his staff decided that the Medical Investigator program was too expensive and placed a moratorium on appointment of new Medical Investigators.

Phase-out of the Regional Research Support Centers

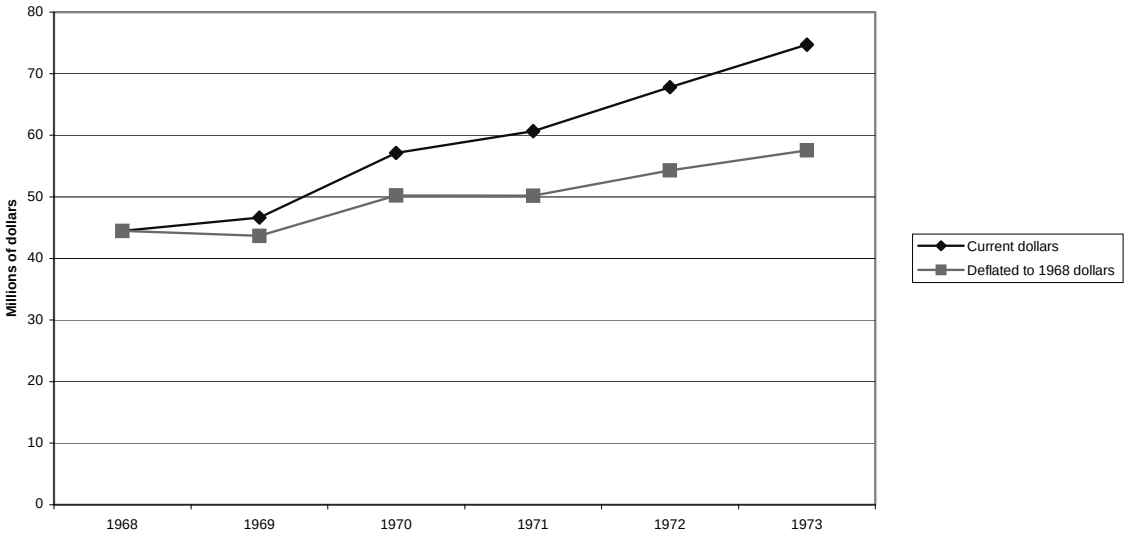
By the time Pittman became ACMD/R&E, the four Research Support Centers had been operating for seven to nine years. Different Centers had developed specific specialties, but all had responsibility for supporting research in every hospital in their section of the country. Unfortunately, the effectiveness of this support appeared to be in inverse proportion to the distance of the Center from the hospitals served, and it became increasingly apparent that much of the function of the Support Center was local rather than general. Also, scientists in the Support Centers wanted to *do* research, not just support it. Moreover, these Centers constituted a rather large and conspicuous budget item. The 1968 National Academy of Sciences-National Research Council review of VA research had recommended that "the Veterans Administration review the programs and accomplishments of its four Research Support Centers to determine whether they are accomplishing the purposes for which they were established and how their assistance to individual investigators can be enhanced."[7]

At the same time, it had become apparent that statistical support beyond that provided by Central Office was needed for the Cooperative Studies Program. Up to this point, studies had been receiving statistical support from many sources, including statisticians from Central Office, the Follow-up Agency, universities and special VA laboratories. To standardize the statistical support of the cooperative studies, the West Haven (Conn.) and Hines (Ill.) Research Support Centers were transformed into Cooperative Studies Program Coordinating Centers (CSPCCs). This transformation was gradual; at first, they continued to do what they had been doing, but increasingly more of their efforts were directed to cooperative studies.

The Western Research Support Center, which had emphasized bioengineering and computing, became the site of the Medical Research Information System (MRIS).[4] For a time, it continued to offer courses in bioengineering and computing, but these tapered off with increasing information system demands. The Southern Research Support Center at Little Rock (Ark.) was disbanded, but some of its staff continued to run the Central Research Instrumentation Pool (CRIP).[24]

In summary, the 1968-1973 period featured strong Central Office attempts to find a research administration design that incorporated peer review and streamlined and rationalized oversight. The goal was to achieve predictably high-quality research while protecting necessary basic research, clinical applications and promising avenues of research. This time of rapid administrative change, much of it controversial, set the stage for the stabilization that followed. At the same time, the research carried out in VA hospitals continued to prosper in the face of the new initiatives. High-quality staff had been hired through the Career Development Program, as had other scientists and clinicians. These factors led to the continuing development of laboratories and research programs in fields important to the care of the Veteran patient.

Figure 15.14 Research budget, 1968-1973



References

1. Telephone interview with Harold Schoolman, M.D., March 1, 1988 and April 26, 1988.

2. Interview with Lionel Bernstein, M.D., Ph.D., November 1, 1988 at Dr. Bernstein's office in Chicago, IL.

3. Interview with Thomas Chalmers, M.D., July 29,1992 at a hotel lobby in Boston, MA.

4. Benjamin B. Wells, M.D., "Circular 10-71-264. VA Medical Research and Education Conference, RCS 15-32-S." 12/9/71.

5. National Academy of Sciences - National Research Council. "Minutes, 25th Meeting of the CVMP." December 5, 1952. Washington, DC: National Research Council, 1952, 522.

6. National Academy of Sciences - National Research Council. "Minutes, 29th Meeting of the CVMP." April 20, 1954. Washington, DC: National Research Council, 1954, 536.

7. National Academy of Sciences - National Research Council. *Evaluation of Biomedical Research and Education in the Veterans Administration.* National Research Council, 1968. 29.

8. Interview with Leon Bernstein, P.D., April 29, 1988 at Dr. Bernstein's home in Alexandria, VA.

9. Interview with Leslie Zieve, M.D., September 21, 1992 at Dr. Zieve's home near Minneapolis, MN.

10. Thomas C. Chalmers, M.D., "R&E Letter 69-5. Institution of new procedures for requesting designated support for individual (research) programs, as Part I of the institutional (research) allocation." 4/15/69.

11. Thomas C. Chalmers, M.D., "R&E Letter 69-9. VA categorical research evaluation committees - Structure, functions and roster of members." 9/11/69.

12. Interview with Gerald Libman, May 5, 1992 at Mr. Libman's home in suburban Maryland.

13. Interview with Abraham Dury, Ph.D., February 8, 1994 at Dr. Dury's home in Florida.

14. Interview with Ralph Casteel, May 3, 1988 at a restaurant in Bethesda, MD.

15. Interview with Lyndon Lee, M.D., April 7, 1988 at a restaurant in Bethesda, MD.

16. Interview with Chester DeLong, Ph.D., May 7, 1992 at Dr. DeLong's Office in VACO.

17. Bailar, J.C., 3rd, "Estrogen therapy for prostatic cancer." *Prog Clin Cancer*, 1970. **4**: 387-392.

18. Interview with John Bailar, M.D., April 29, 1988 at Dr. Bailar's office in Washington, DC.

19. Telephone interviews with Thomas Newcomb, M.D., March 15, 1988 and May 28, 1988.

20. M.J. Musser, M.D., "Chief Medical Director's Letter IL 10-71-17. Revision of VA Research Program." 3/9/71.

21. Interview with James Pittman, M.D., February 27, 1992 at Dr. Pittman's office in the Dean's Office at the University of Alabama School of Medicine.

22. Lyndon E. Lee, M.D., "R&E Letter. Phase out of disapproved Part I research programs." 7/10/70.

23. Interview with Thomas Newcomb, M.D., March 29, 1992 at a hotel lobby in Washington, DC.

24. Benjamin B. Wells, M.D., "R&E Letter 66-3. Central Research Instrument Pool." 6/21/66.

(Intentionally Blank)

Chapter 16. Medical Research in VA Comes of Age, 1974–1980

On the heels of increasingly complex organizational demands, a time had come for a genuine maturation of research as an institutional entity within VA. Although new opportunities to acquire personnel and funding had been widely welcomed, they had been accompanied by inevitable growing pains. A crucial era had arrived. VA's leaders would be tested to effectively shape the research program into a stable enterprise that would not only encourage its participants, but also foster recognition and support for the future.

During this time, a subtle but significant change was made in the nomenclature of facilities within the VA health care system. The longstanding term "hospital" was abandoned in favor of "medical center," seen as more representative of the range of activities, including research, that was present at most VA locations.

Reorganization of Research and Development

As the activities of the Research Service, and simultaneously the Education Service, expanded and became more diverse, demands on the ACMD for Research and Education increased. There was a feeling, especially among the Education Service staff, that the needs of Research Service received preference in the R&E Office. Laurence Foye, M.D., Director of Education Service, campaigned to establish a separate Office of Academic Affairs.[1] He was successful when the Department of Medicine and Surgery was reorganized during the Nixon Administration. This reorganization coincided with James Pittman's departure in mid-1973 to become Dean of the Medical School at the University of Alabama. After the reorganization, the Offices of Academic Affairs and Research and Development were separate, with Foye and Thomas Newcomb as their respective ACMDs. The new office of Research and Development now comprised two Services and maintained a "staff office." The Medical Research Service, the former Research Service, searched for a new Director to replace Newcomb. Carleton Evans, M.D., directed a revitalized Health Services Research and Development Service (Chapter 19), an outgrowth of the old administrative research and hospital computer programs. The Prosthetics Research Program, which originated as a staff office, would soon become a separate Service (Chapter 20).

Organization of the Medical Research Service in 1974

In April 1974, the author joined VA Central Office as Director, Medical Research Service. Her former position—ACOS/R&D at the Buffalo (N.Y.) VA Hospital had provided experience working within the VA research milieu, and appointments to several advisory groups and site visit teams, including one as chair of an original RRAG group, added specific familiarity with the Central Office research staff.

In 1974, the Medical Research Service staff was much slimmer than the Research Service of the 1960s. Program Chiefs no longer provided a strong professional presence, and their support staffs had been reassigned. In fact, the new Medical Research Service had only two physicians, a veterinarian and three Ph.D. scientists. Abraham Dury, Ph.D., who had previously been Program Chief for Basic Sciences (Chapter 12), was the Deputy Director and had been effectively running the Service, while the new ACMD/R&D, Dr. Thomas Newcomb, was focused on building new

programs. Four staff assistants—one for each geographic region—handled day-to-day funding decisions, after consulting with Dury. Darlene Whorley was quietly and effectively running the Career Development Program, and Gerald Libman, assisted by two other executive secretaries and a small support staff, had stabilized the Merit Review program.

Figure 16.1. Marguerite Hays, M.D.

James Hagans, M.D., Ph.D., was heading the Cooperative Studies Program from his Miami office, assisted by Marian Brault in Washington. He worked vigorously to mold this program, which changed in many ways during the 1970s (Chapter 18).

The Field Operations section administered undesignated research funds sent to the hospitals, which made up most of the budget. A hospital's research budget was still largely based upon precedent, derived from the previous year's budget, with adjustments that took into account new RRAG and Merit Review approvals. Even though many new funding decisions could now rely on RRAG recommendations, requests for new funding abounded. During the first few months after the author arrived, numerous visits were made by special pleaders; it was essential to stabilize the funding mechanism. The author appointed Elston Hooper, Ph.D., who had long experience and a deep understanding of the research program, to be Chief, Field Operations. In this new position, Hooper assumed the role that in the 1960s was that of the four Regional Coordinators and more recently of Dr. Dury himself. Hooper served as a buffer between the author and the "special pleaders."

Figure 16.2. H. Elston Hooper, Ph.D.

The Central Office staff members were bombarded by requests for expensive new and replacement equipment, and found these requests difficult to evaluate. An early decision was to appoint Gerald Hine, Ph.D., an instrumentation expert in his discipline of nuclear medicine, to review and administer research instrumentation.

Figure 16.3. Gerald Hine, Ph.D

Based on her experience as ACOS/R&D at Buffalo, the author was primarily concerned about two problems with the administration of the Medical Research Service. The first was its relative lack of flexibility: a hospital's research budget tended to remain stable even though its programs varied. This made it difficult for a growing program to emerge successfully. On the other hand, the status quo was a highly satisfactory situation for a well-established research program, and especially for one with declining activity. A budgeting scheme was needed that was transparent—one based on discernible factors that reflected a hospital's current research activities.

Another concern was the general confusion in the field resulting from the many recent major policy changes. Most of the ACOSs were themselves unclear about current research policy and that uncertainty was amplified in the minds of the investigators they were supposed to be guiding. The program needed consistent policies that were acceptable to all interested parties in Central Office, acceptable in the field, and understood by all. It was vital that those most affected by policy changes—hospital researchers—had a clear understanding of the policies that would govern them.

The Central Office Medical Research staff devoted considerable effort to describing policies explicitly and distributing the information to the field in clearly stated circulars and letters. Research was still officially functioning under a 1962 procedural manual so outdated that no one ever referred to it. It took the coordinated efforts of many within Central Office to completely review and process needed changes culminating in the issuance of a new manual in the early 1980s.

Establishing a management information system as the basis for the research budget

To make hospital research budgets more responsive to current activity, the author, Dury and Hooper worked with the staff of the Sepulveda (Calif.) Bioengineering and Computer Center (BECC) to expand and upgrade the Medical Research Information System, MRIS (which was soon expanded to include all of R&D and renamed the Research and Development

Information System, RDIS[2]).

Figure 16.4. Frederick Weibell, Ph.D. Chief of the BECC

At that time, except for the Automated Hospital Information System (AHIS) at the Washington, D.C., VA Hospital (Chapter 19), no management information system existed in the VA medical program, and a congressional restriction forbade the purchase of new computers. Fortunately, Research already owned a computer at the BECC. Although antiquated—it used punched cards and was programmed in Fortran[2]—it was available. So this was the machine drafted to support the original RDIS.

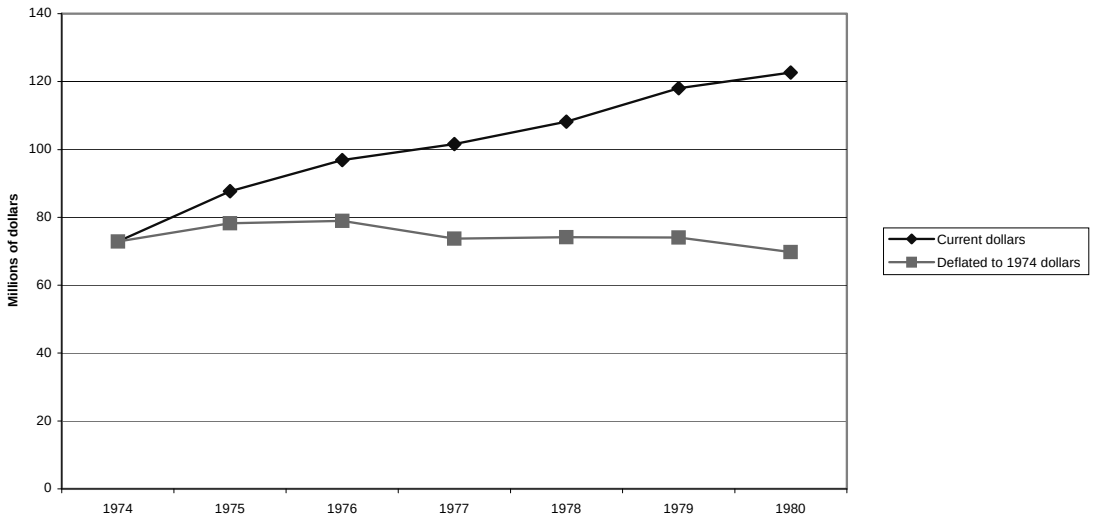
In the new information system, each project was simultaneously reported to RDIS and the Smithsonian Science Information Exchange (SSIE). SSIE coded the projects and sent these codes, along with project summaries, to the BECC. Each project was then cross-tabulated in budgetary reports to a specific part of the medical center's research budget. Other parts of the new system provided information about the numbers of principal investigators, the numbers of users engaged in animal studies, and the numbers of users of common resources at each hospital. Over several years, the system was revised until it was possible to combine this information with the results of Merit Review, RRAG review, the salaries of basic research scientists, Career Development Awards, Cooperative Studies activities and special laboratories, to establish a total hospital research budget.

Common resources

The major "soft," and the most controversial, area in this budgetary scheme was the amount of core support or "common resources" to be allocated to each medical center's research budget. These common resources were the residual from the old "Part 2" funds and sometimes constituted the majority of a hospital's research budget. Working with advisors, the Medical Research Service established formulas for the appropriate funding for each common resource, based upon such factors as the number of investigators using that particular resource and the size of the total program. Using this analysis, the BECC calculated the projected funding for common resources for the various medical centers and then compared the results with each hospital's existing funding level. In some cases, the discrepancies were great. It was decided to make gradual adjustments toward achieving equity, aiming for full implementation of the formula within five years.

The more alert ACOSs quickly caught on to this new system. New common resources began to appear in their annual reports. When these were the same as in most other hospitals, they were simply added into the formula. However, unique common resources also appeared, and it was difficult to decide whether they were appropriate. The RRAG groups tried to advise about them, but they found this difficult without on-site investigation. Later, site visits by the Research Advisory Committee helped influence these decisions.

Figure 16.5 Medical research budget, 1974-1980



Establishing new budgetary policies

In the late 1970s, one budget crisis occurred after another. At the same time that inflation-corrected dollars were shrinking (Figure 16.5), the number of qualified researchers seeking support was increasing. For several years, these budgetary strictures were met primarily by cutting back on non-Merit Reviewed programs. Under the decentralized program of the early 1970s, Merit Review success had been rewarded with increased funding, yet lack of success had not resulted in decreases. A number of investigators continued to be supported from the "basic institutional support" at the medical centers, without applying to the Merit Review program, a carryover from "Part 2" funds. Many of these persons had never applied for Merit Review approval of their research.

The author worked with Dr. Newcomb to communicate with others in Central Office about the problems and how they were being addressed. Policy changes were openly debated within Research and Development. At that time, John Chase, M.D., the Chief Medical Director, held daily staff meetings, which were attended by all the ACMDs as well as other key officials. These meetings provided an opportunity to discuss significant new events and possible policy changes. Newcomb received early feedback from those who were unhappy with proposed changes, allowing room to negotiate. They also talked to many ACOSs, during visits in both directions, phone calls and formal meetings. The ACOSs' annual meetings included extensive open discussion of policy issues.

A system gradually evolved in which most of a hospital's research funding was based upon Merit Review. The first step in this process was simply to inform the hospitals how their budgets had been calculated. The BECC group performed these calculations, using the RDIS budget report, which showed the calculations, including details about common resources. Funding for investigators appeared in various columns: "RAG," "Merit Review approved," "Merit Review disapproved" and "not reviewed." Some ACOSs strongly protested identifying their budgets in this degree of detail, preferring the previous vagueness, which allowed more room for manipulation. But most seemed to prefer a transparent budgeting system.

Once the basis of the budget was explicit, budget policy shifted. Except for very small programs, continuing programs were required to undergo Merit Review. Once this requirement had been widely announced and had survived intense debate, programs that had not yet been submitted for review were not funded. This caused turmoil among those who believed they could rely on political considerations to retain their funding. While the author and Dr. Dury tried to be as flexible and empathetic as possible in enforcing these new policies, they did indeed enforce them. Unlike the situation faced by the research leaders of the late 1960s, whose policies were reversed by their organizational superiors, Newcomb and CMD Chase were consistently supportive and never reversed decisions made in Medical Research Service, despite political pressure to do so.

Once the principle of peer review for all individual programs was firmly in place, programs that failed peer review had to be dealt with. This was even more traumatic for participants than the actual review. Support of disapproved programs was tapered off gradually, to give investigators another chance to apply without closing down the project. The goal was to maintain the continuity important to an intramural program.

In 1974, when this change in funding policy began, the National Academy of Sciences (NAS) was just beginning its third review of the VA Research program. The review was eventually published in 1977, which in retrospect was an unfortunate time for publication, as funding policies were in flux. Some of the policies the committee criticized had already changed by the time of their final report. The NAS group was particularly concerned that disapproved programs were being supported at the local level.

As funding grew tighter, money was insufficient to fully fund even approved programs. Agencies funding extramural programs can deal with this problem by funding only programs receiving the best evaluations from their reviewers. However, the author and Dury believed, as had Lionel Bernstein and Leon Bernstein, that an intramural program should fund all of its peer-review-approved projects. If a program was not good enough to fund, the Merit Review Board should disapprove it. But when there is not enough money to fund all meritorious programs fully, the only alternatives are to exclude some of them or to reduce the amount of money awarded to each, the choice made by Medical Research Service. To do this, a sliding scale reflecting the priorities assigned by the Merit Review Boards was built into the computer program used in calculating the budget

After 1975, the budget was a constant problem. VA was working hard to upgrade its patient

care program, and attention was directed to medical care rather than to the research program. Some years, the research budget seemed a "sacrificial lamb" to achieve badly needed increases in the patient care budget. This budgetary squeeze finally led, in 1978, to a proposal that VA cut off funding to many hospitals with small research programs (Chapter 17).

The OMB study of VA peer review

As VA's Merit Review Boards worked to gain OMB charters, a problem arose: OMB staff began to feel that VA, through its Merit Review Boards, was mimicking the NIH and its grants program. Newcomb's response was that the VA merit review system was simply the application of quality control in an intramural system, which was very different from NIH's extramural grants program.

During the negotiation with OMB that eventually led to chartering the Merit Review Boards in 1972, the OMB staff required that VA and NIH conduct a joint "experiment" on peer review. This study, conducted in 1974 and 1975, compared the work of the VA Merit Review Boards with that of NIH Study Sections. Gerald Libman and his VA Program Review staff worked with the Executive Secretaries at the NIH to perform a blinded double review of VA projects. Applications to the NIH by VA staff were duplicated and sent to VA, with VA cover sheets. Comparable VA Merit Review applications were sent to the NIH, with NIH cover sheets, to enter into the NIH review process.[3] Eventually, the NIH abandoned the study; many NIH staff were involved, often each with only one study project to handle, and they found the experiment to be too time-consuming and confusing. Anecdotally, in reviewing the results of the aborted study, VA was reassured about the quality of its Merit Review Boards. In most cases, the two agencies' reviews were similar. When they differed, discrepancies tended to balance out, with some VA projects receiving better VA reviews and others better NIH reviews.[4] Though funding of VA applications was based only on VA results, some investigators felt that they were placed under double jeopardy. By the time the experiment was abandoned, the staff at the OMB had changed; the new staff did not pursue the study and allowed continuation of the Merit Review Boards.[5]

Changes in the Merit Review system

Secondary review

As the results of Merit Review grew increasingly important to VA's medical centers, a great deal of interest naturally centered on the reviews. In the early days, considerable pressure was applied to use the Director's executive authority to reverse disapproval decisions. In the mid-1970s, Medical Research Service established a second level of review, by a "Medical Research Council," consisting of Medical Research Service senior staff and others in Central Office interested in research. The Council members reviewed all Merit Reviews, scrutinizing Merit Review Board recommendations one by one. When reviewers felt that the Board's recommendation might have gone astray, they would recommend that the proposal be returned for additional review, perhaps by a different Board. The final decision was left to the Director, and on rare occasions the author reversed a disapproval decision.

Investigators in medical disciplines that lacked a Merit Review Board in their specific subject areas frequently complained that they were not receiving a fair review, although expert reviewers were always sought. While this problem plagues all peer-review systems, even at NIH, for VA the difficulty was compounded because fewer Boards existed so each Board was expected to cover a broad area. Since most nuclear medicine proposals were cross-disciplinary, they were generally reviewed by whatever specialty board seemed best suited to review them. After one round of Merit Review in which the performance of nuclear medicine proposals had been dismal, a special advisory group of nuclear medicine specialists re-reviewed the proposals. These reviewers were informed of the actions of the primary boards and were asked to look for possible areas of unfairness. In virtually every case, however, they endorsed the Boards' original decision. There is no way to know what their decisions would have been had they served as the primary review group.

Appeals

With so much now depending on Merit Review Board decisions, an investigator needed to be able to appeal a Board decision. But since unjustified appeals could swamp the system, only limited types of appeal were allowed.[6] An in-house committee reviewed appeals with advice from the Program Specialists, but this mechanism did not work well. With staff members unenthusiastic about appeals, very few of them were upheld.

Type 2, 3 and 4 Merit Review proposals

Another innovation that was not very successful was the introduction of three new types of Merit Review proposal. In addition to the standard ("Type 1") proposal, which included a full description of proposed research, the new Type 2 and Type 3 proposals were to be reviewed retrospectively. Type 2 proposals were for small projects funded at less than $25,000 yearly, in which the request was simply for continued funding at the existing level. Any ongoing program under $25,000 was eligible for Type 2 review. To be eligible for Type 3 review, the retrospective review of larger programs, the principal investigator needed to have been funded in VA's research program for at least 10 years. Type 4 proposals were for pilot projects costing less than $25,000.

The retrospective review of Type 3 programs fit the concept that a senior investigator who is consistently productive should be supported based on track record without the need to present a complex prospective research program. Some of the leading ACOSs favored this approach, and Rosalyn Yalow was a strong advocate. There was enthusiasm in the field, and Central Office received many Type 3 proposals. However, the Merit Review Boards frequently turned them down, owing to the absence of a prospective proposal. Even though Board members had been instructed about the criteria for Type 3 proposals and understood that they were supposed to be reviewing them retrospectively, they were uncomfortable without a complete prospective proposal to review. Other mechanisms for reviewing these proposals were considered, such as a bibliographic analysis. For one round, the RAG groups, rather than the Merit Review Boards, reviewed them. The RAG groups, however, were also uncomfortable with this new assignment. Eventually, early in the 1980s, the retrospective review alternatives were abandoned. As with the appeals mechanism, the concepts of Type 2,

3 and 4 reviews failed primarily because they were not well accepted by those whose job it was to implement them.

The Research Career Scientist Program

After a few years of the new budget policies, a number of independent Ph.D. scientists whose salaries had been built into their hospitals' budgets lost their research funding. This presented the anomaly of a person being paid to conduct research who had no support for the research itself. As most of these researchers had been hired into government career appointments, it was not possible simply to terminate their appointments. Yet one could not justify continuing to pay their salaries. In 1977, Medical Research Service notified the medical centers where these unfunded scientists were located that unless they had achieved peer-reviewed research funding (VA or non-VA) by the beginning of the following fiscal year, the hospitals would receive no money for their salaries. Approximately 25 individuals were affected, and this decision generated great concern. However, the medical centers handled this crisis very well. Some of the scientists who were eligible to retire did so. Others stepped into other jobs at the hospital. A number of them said later that they were happier in their new positions.

Clearly, it was desirable to avoid a recurrence of this situation. A new policy stated that, in the future, new non-clinician scientists could be hired into a career appointment only if they qualified for a new category entitled Research Career Scientist.[7, 8] A Research Career Scientist appointment honored the most successful non-clinician scientists already within VA and provided a means of recruiting new "superstars." A new committee reviewed applications, using criteria similar to those used by universities evaluating candidates for tenure. This committee set such high standards VA hospitals soon boasted an elite corps of research stars (Appendix VIII).

The Research Career Development Program

In 1975, VA physician's bonus was introduced. Previously, VA physicians' salaries had been fixed at the same level as other employees in the equivalent Civil Service grade. As a consequence, their salaries lagged so far behind those of physicians at other institutions that it was becoming very difficult to hire first-rate physicians into VA. The research program at that time was essential for recruiting and retaining physicians, and withholding research funds from an important clinician was controversial. The introduction of a bonus, however, made physicians' salaries competitive with academic salaries, at least for a time. As a result, outstanding physician-scientists flocked into VA, and Medical Research Service had many new applications from talented investigators. This influx of talent occurred at the same time that the budget's spending power began to decline.

One problem imposed by the physician's bonus affected the Research Career Development Program. Since the bonus was specifically directed to correct recruitment problems and vigorous competition existed for Career Development positions, there was no problem in recruiting persons into that program. For this reason, CMD Chase made an agreement with OMB staff that, if they would approve the physician's bonus, he was willing to exclude from that bonus certain categories of physicians.[9] These categories included the Career

Development physicians. Suddenly, Research Associates, Clinical Investigators and Medical Investigators, who had been paid the same as their peers in the clinical services at their hospitals, were being paid considerably less. The consequence was a significant exodus from the program, particularly among the more senior persons, who took high-level positions at their medical centers, where they were eligible for the bonus. Some hospitals that had been active in nominating persons into the Career Development Program dropped out. Others, particularly when an affiliated medical school was willing to help make up the salary difference, continued to present outstanding candidates for Career Development positions. It turned out that many highly qualified young physicians were sufficiently interested in a research career that they were willing to accept smaller salaries in exchange for having extra time for research. The program continued to flourish.

The Research Career Development program had become so popular that the qualifications of successful candidates continued to escalate. When the Clinical Investigator program was introduced in the late 1950s, it was considered to be an entry-level program (Chapter 7). But as Clinical Investigator positions became increasingly competitive, and applicants' qualifications grew increasingly more impressive, a gap was left at the entry level. In the 1960s (Chapter 12), this gap was filled by applicants for the Research Associate position. By the mid-1970s, qualification for the Research Associate position had escalated to the point that it was no longer accessible to truly entry-level persons. In fact, the rather modest research support that came with the appointment was only a fraction of the total support of some successful candidates. Most of them also applied for Merit Review and many for other sources of funding. In some instances, Clinical Investigators were running huge laboratories with a large number of staff, quite inappropriate for a person still in a developmental career phase. In hopes of discouraging fully independent investigators from pushing the "developing" investigators out of the Research Associate and Clinical Investigator slots, limits were placed on their funding. While this discouraged some over-qualified individuals, these positions continued to be very popular among well-qualified researchers.[10]

Once again there was a need for entry-level positions in the Research Career Development Program. In setting up the new appointment level, constraints were placed to prevent it from also escalating and becoming filled with over-qualified incumbents. Only clinicians without research training except that incidental to their residencies were eligible. This new position was a two-year appointment, with one-year appointments available to those who had completed one-year research fellowships. Those with both M.D. and Ph.D.degrees were not eligible, as they had already benefited from research training. To further emphasize this as a junior position, successful candidates were salaried lower than the usual staff-physician levels, and were ineligible for the physician's bonus.[11]

Despite these constraints, good candidates soon applied for appointment to the new position of Associate Investigator. A major problem in their review was the nature of the research protocol itself. It was understood that these inexperienced candidates needed some help in writing their proposals. It became obvious that in some cases the preceptor had actually written the proposal; in others, the candidates themselves wrote it. Given this disparity, it was sometimes hard for the Career Development Committee to assess candidates. Increasingly, they emphasized their preference for a good (but not necessarily polished) proposal with

evidence that the candidate had written it.

The Career Development program was always considered important, and it received preferential funding. Until the mid-1970s, all approved applications were funded. However, with the budget squeeze of the 1970s, it became necessary to use priority cutoffs that became progressively restrictive. By the time the Associate Investigator position was introduced, even it required a priority cutoff, though it was more lenient than for the more senior positions. So it was introduced in a modest way, and funding of Associate Investigator positions was always very competitive.

Newcomb and the author decided to reintroduce the Medical Investigator position, which had been under a moratorium for new appointments, by accepting limited numbers of applications starting in 1975. One problem had been that these expensive positions tended to be grouped in a few successful hospitals. This did not seem equitable, particularly since these mature and successful clinician-scientists could be important influences in hospitals with small research programs. In reintroducing the Medical Investigator position, its character was changed in a number of ways: (1) Only clinicians already on the VA staff could apply. (2) Each hospital had a limit of two Medical Investigators at any one time. (3) The appointment was for six years and could not be renewed unless the investigator had spent at least one year on the clinical staff at the completion of the earlier appointment. (4) In nominating a Medical Investigator, the hospital management had to promise to rehire that person on the clinical staff at the end of the appointment. In addition, at that time, Medical Investigators were ineligible for the physician's bonus. Nevertheless, once the position was reopened, applications flooded in. Generally, not more than one or two of these expensive appointments were made at each semiannual round of Career Development reviews.

Changes were also made in the Senior Medical Investigator program. Ludwig Gross and Oscar Auerbach both reached their 70th birthdays in 1975 and faced the then-mandatory retirement from VA. They could no longer be Senior Medical Investigators, but VA honored them as Senior Medical Investigator Emeriti and as Distinguished Physicians, an appointment available to retirees. Both continued to conduct research at their hospitals. These two vacancies made it possible to think about appointing new Senior Medical Investigators. William Oldendorf at Brentwood (Calif.) was made Senior Medical Investigator in 1978, and Roger Unger from Dallas, previously ACOS for Research, received the appointment in 1979.[12]

Middleton Awardees

The 1974 and 1975 Middleton Awards were presented in VA Central Office with key officials present.

The 1974 awardee was Paul Srere, Ph.D., from the Dallas VA Hospital, for his biochemical accomplishments on key cellular metabolic pathways regulating lipid and carbohydrate synthesis and storage. Dr. Srere was in one of the first group of Research Career Scientists to be appointed and was an active and valued advisor of the research program.

Figure 16.6. (left to right): Chief Medical Director Chase, Middleton Awardee Paul Srere and Administrator Richard Roudebush

In 1975, Paul Heller, M.D., of the Chicago West Side VA Hospital was honored with the Middleton Award. Heller was a Czech who, after six years in Nazi concentration camps, had been able to come to the United States to finish his training and had then made a career in VA. He led VA's important cooperative study on the sickle-cell trait. The Middleton Award honored him for his research in hematology, immunology, enzymology and metabolism, including findings on the mechanism of immunologic deficiency in multiple myeloma.

For the next three years, the award was presented at a celebration held in conjunction with a meeting of research administrators and advisors. In 1976, it went to William Oldendorf, M.D., from the Brentwood VA Hospital in Los Angeles for his development of nuclear techniques in clinical neurology. These included the first description of computerized tomography, the development of techniques of cerebral blood flow measurement, elaboration of cerebrospinal fluid functions and characterization of blood brain barrier permeability. The first of these accomplishments , computerized tomography, was the basis of his 1975 Lasker Award and his later nomination for the Nobel Prize.

Oldendorf's introduction to VA research while he was Chief of Neurology at the Los Angeles VA Hospital clearly reflected the less structured, more personal approach to funding sometimes seen in earlier years. In a 1991 interview, he described being approached by Morton Grossman, the hospital's acting research chief, who asked, "Bill, you're interested in research aren't you?" Oldendorf recalled what happened when he confirmed he was interested in doing research with a simple "yeah."

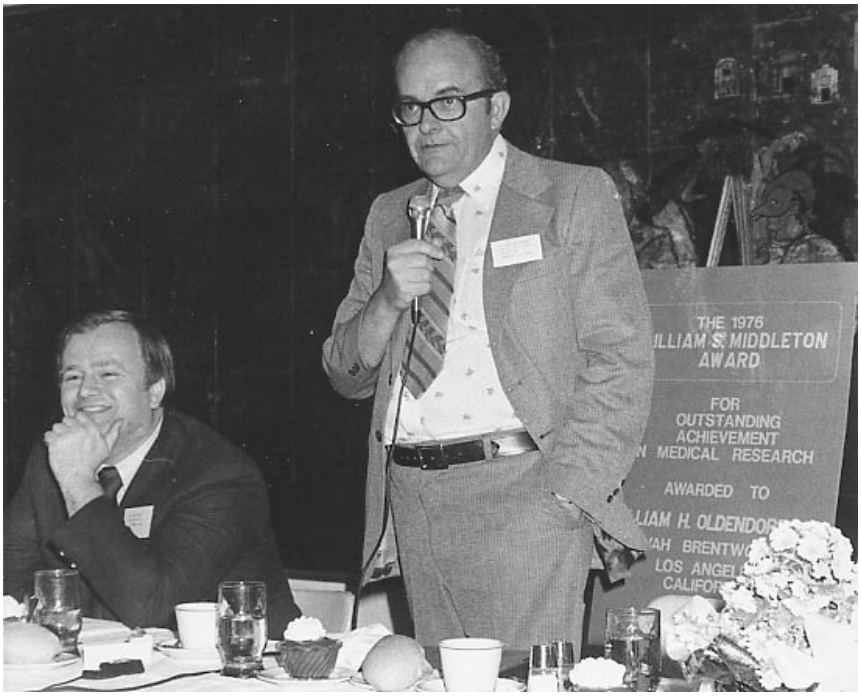


Figure 16.7. William Oldendorf accepting the Middleton Award as Administrator Max Cleland smiles

> "He (Grossman) said, 'Have you got any funding?' and I said, 'No.' Then he asked, 'Could you use $3,000?'
>
> "Could I! And so I had an account of 3,000 bucks set up. With that, I got a double sodium iodine head detector made up. And I did all that old work with the boluses measuring blood flow going through the head. And I used the same funds to build the first CT scanner...Did everything myself."[13]

Oldendorf conceived the idea for the CT scanner as a way to avoid the pain and complications suffered by patients who had to be studied by pneumoencephalography to detect brain lesions. He set up the prototype scanner in the den at his home, using, among other things, an old model railroad train track.

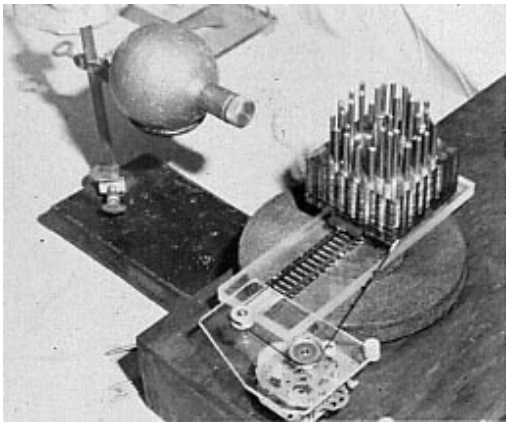


Figure 16.8. The prototype for the CT scanner

Figure 16.9. Oldendorf in his den in 1961 with the CT scanner prototype

In 1977, Charles Lieber, M.D., of the Bronx (N.Y.) VA Medical Center received the Middleton Award for his studies of the toxicity of alcohol, including elucidation of its interaction with drug, lipid and uric-acid metabolism, and the pathogenesis of fatty liver and cirrhosis in humans and nonhuman primates.

Figure 16.10. Charles Lieber, M.D.

The 1978 award went to Victor Herbert, M.D., also of the Bronx, for "developing scientific tools to diagnose nutrient deficiencies, measure nutrient binding proteins, demonstrate selective deficiency of nutrients in one cell line but not another, and applying the scientific criteria of safety and efficacy to nutrition folklore."

In 1979, Edward Freis, M.D. (Chapter 9) received the award for his "studies of hypertension that proved the efficacy and life saving qualities of medical treatment."

Figure 16.11. Norman Talal, M.D., receiving the Middleton Award From Acting Administrator Rufus Wilson

Norman Talal, M.D., a Medical Investigator at the San Francisco VA Medical Center, received the 1980 award in a VACO ceremony from Acting Administrator Rufus Wilson. He was cited "for the development of immunological concepts derived from the study of patients and animal models for autoimmune and endocrine systems which has led to new theoretical and therapeutic considerations for human diseases."

New honors for VA researchers

In addition to VA's own Middleton Award, in the 1970s VA researchers were honored with many prestigious awards, including five Lasker Awards and two Nobel Prizes.

Lasker Awards

After the Nobel Prize, the Lasker Award is arguably the top honor for an American medical researcher. Edward Fries, M.D., received the Lasker Award in 1972 for "his demonstration of the life-saving effectiveness of drugs in the treatment of moderate hypertension" (Chapter 9). Ludwig Gross, M.D., of the Bronx, won it in 1974 for "his original discovery of leukemia- and cancer-inducing viruses in mammals, and the elucidation of their biology and epidemiology" (Chapter 3). And recognizing his original concept of the principles demonstrating the feasibility of computerized tomographic scanning, William Oldendorf, M.D., won it in 1975 for "discoveries which have envisaged a revolution in radiology".

According to the Lasker Foundation, more than half of those honored with the Lasker Award for Basic Medical Research since 1962 later received the Nobel Prize. This was true of VA's Nobel Prize laureates Rosalyn Yalow and Andrew Schally, both also honored with Lasker Awards. Schally won the Lasker Award in 1975, cited as one "whose research has expanded our knowledge of the interplay between the hypothalamus and the endocrine system." Yalow's 1976 Lasker Award was "for the discovery and development of the technique of radioimmunoassay" (Chapter 11).

Figure 16.12. Celebration at the Bronx VA Medical Center the day Rosalyn Yalow heard she would receive the Nobel Prize: (Left to right) Ludwig Gross, Bernard Roswit, Rosalyn Yalow, Thomas Chalmers (Dean, Mt. Sinai School of Medicine), Julius Wolf (Chief of Staff), Bernard Straus (former Chief of Medicine who had helped Yalow recruit Berson), Marguerite Hays and Herbert Rose (ACOS/R&D).

Nobel Prize

In 1977, Rosalyn Yalow from the Bronx and Andrew Schally from New Orleans were awarded the Nobel Prize. This was a time of great excitement in VA's Research and Development office. On the day the prizes were announced, the author went to the Bronx for a celebration in the afternoon and both she and Newcomb attended an evening celebration in New Orleans. Later, VA held a reception at the Capitol in honor of its Nobel laureates. Schally was received by the King of Spain shortly after the Prize ceremony. Both later received many honorary degrees.

The two winners had rather different reactions to the honor. Schally quickly dug back into his laboratory, determined, as he put it, to win a second Nobel Prize. Yalow, on the other hand, took her prize as an opportunity to support the VA research program that had supported her. She declared widely that she had never applied for NIH funding but had depended entirely on VA for support of her laboratory.

Yalow campaigned for VA research funds at the level of Administrator in VA, and also with Congress. To the Central Office Research staff, her efforts were a mixed blessing. Certainly, the VA research effort needed the publicity and the exposure she provided. On the other

hand, she was strongly opposed to the use of peer review for evaluation of research and expressed her opinion freely and in high places.

Figure 16.13. Andrew Schally (second from left) next to King Juan Carlos I of Spain

After discussions with Yalow about research administration, VA Administrator Max Cleland appointed a special research advisory committee, which Yalow chaired. The committee included Edward Rall, M.D., head of the intramural program at NIH, Julius Axelrod, Ph.D.,Nobel laureate from NIH, Morton Grossman, M.D., Ph.D., VA Senior Medical Investigator, and a few others of similar distinction. The committee reviewed the medical research program, its current status and the way it was administered. They learned about the Career Development Program, Cooperative Studies and the new high-priority programs, but their primary interest was the Merit Review system. The committee reviewed it in considerable detail, paying particular attention to the way results were used. In the end, the committee not only rejected the idea of abolishing the Merit Review program, but some of the visitors favored abruptly discontinuing disapproved programs.

Personnel changes

Dr. Abraham Dury retired in 1976 and, after a nationwide search for a new Deputy Director of Medical Research Service, Elston Hooper assumed the position. In 1978, Betty Uzman, M.D., who was then the ACOS/R&D at Shreveport (La.) offered to come to Central Office if she was needed. A person of her talents was certainly needed, but there was no appropriate staff opening at the time. She joined Central Office as “Assistant Chief of Field Operations.”

Soon, the incumbent Chief transferred to a different job and Uzman became Chief. Under her guidance, the Field Operations program became systematic and responsive to the field. She saw to it that policies were clear and decisions as fair as possible. Uzman was a strong advocate of peer review and opposed any administrative adjustment to Merit Review recommendations.

Figure 16.14. Betty Uzman, M.D.

When Elston Hooper retired in late 1978, Earl Freed, Ph.D., became the new Deputy Director of Medical Research Service. In his previous position of research coordinator in the Mental Health and Behavioral Sciences Service in Central Office, Freed had achieved good relations with Medical Research Service. He had been a successful research investigator for many years at the Lyons (N.J.) VA Hospital and consequently understood the requirements of psychology research and the research needs of the unaffiliated hospitals.

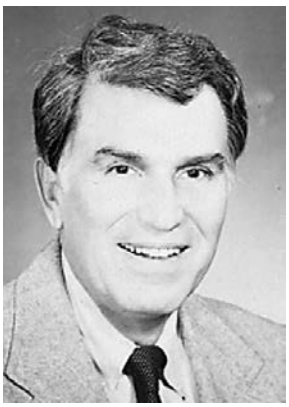


Figure 16.15. Earl Freed, Ph.D.

Mr. Wayne Tippets, Administrative Officer for Medical Research Service from 1974 to 1978, entered the program to become a Medical Center Director, and Mr. Dennis Roth became Administrative Officer. Roth later became Administrative Officer for the ACMD/R&D and remained in that taxing position into the 1990s.

Figure 16.16 Dennis Roth and Wayne Tippets

When Gerald Libman moved in 1977 from his position as Chief of the Program Review Division, the unit that administered the Merit Review program, Jane Schultz, Ph.D., a scientist from the Ann Arbor (Mich.) VA Medical Center, became Chief. When she returned to her laboratory in 1979, Howard Berman, Ph.D. assumed the leadership of that complex operation.

In the summer of 1978, Newcomb left Central Office for San Antonio (TX) to be Chief of Staff at the VA Medical Center there and Associate Dean of the University of Texas, San Antonio medical school. At about the same time, Dr. Chase completed his four-year term as Chief Medical Director and left Central Office. After a search that lasted several months, Administrator Cleland named James C. Crutcher, M.D., from the Atlanta VA Medical Center, as CMD. Crutcher was an unexpected choice, as he had no Central Office experience. He had been Chief of Medicine for many years at Atlanta and more recently had been ACOS for Education. He was also a Brigadier General in the Army Reserve. Laurence Foye had left shortly before Chase, so the Deputy CMD position was also vacant. Crutcher asked Donald Custis, M.D., a retired Navy Vice Admiral, at that time Deputy ACMD for Academic Affairs, to serve as Deputy CMD. After he had been in Washington for several months, Crutcher appointed the author to the ACMD/R&D position. Betty Uzman then became Director, Medical Research Service.

Figure 16.17. Jane Schultz, Ph.D.

Figure 16.18. Howard Berman

The Innovative Research Program

While her appointment to the ACMD/R&D position was being considered, the author, with Chief Medical Director Crutcher and Administrator Cleland, met with Senator Alan Cranston. Cranston, Chairman of the Senate Veterans Affairs Committee, was a very powerful figure in Veterans' politics. Rosalyn Yalow had many conversations with him about her ideas on research. Cranston's keen interest in the VA research program was apparent, as he inquired about research philosophy and, in particular, about attitudes toward peer review. He asked how the research leaders were making allowances for innovative programs that might not be recognized by the peer-review groups. Later, Cleland learned that the Senator was willing to agree to the author's appointment on the condition that 2 percent of the VA research budget be set aside for "innovative programs."

Uzman and the author worked together to establish an "Innovative Research" program within the constraints of the research budget and the peer-review system. Much of this requirement could be met within the current Merit Review system by identifying particularly innovative programs with the help of the Merit Review Boards; these innovative programs would then be funded preferentially. A separate category in the RDIS budgeting system was established to accommodate this preferential funding.

The Research Program Specialists sorted through current projects in their areas searching for innovative programs. The Merit Review Boards identified projects they considered particularly innovative. A letter to the field announced this new "innovative research" program and invited persons who felt their research to be particularly innovative to write. While these projects never quite added up to the Senator Cranston's 2 percent requirement, making inquiries from his staff a bit awkward, a sincere attempt was made to meet it without violating the principle of peer review.

Special Emphasis Areas

An effort had always been made to direct VA research money to solving health problems of greatest importance to Veterans. The centrally directed research programs of the 1920s and 1930s narrowly focused on such problems. During the post-World War II period, with university affiliations, this effort was less direct. Pragmatically, if a VA doctor could justify a research project on scientific grounds, VA supported it. In most cases, these projects were relevant to the Veteran, because Veterans were the patients of these doctors. In addition, focused programs were undertaken, including those of the Advisory Committee on Aging Research and the centralized programs on prosthetics, tuberculosis and psychiatric disease.

Nevertheless, by the mid-1970s, with implementation of peer review and depletion of Central Office professional research staff, little effective effort was being devoted to boosting VA-supported research in the areas of particular importance to the Veteran patient. It became

difficult to respond constructively to the ever-present pressures from Congress and influential groups to divert research funds into their areas of particular interest. It seemed wise to define some explicit research priorities oriented to the special needs of the VA patient.[14] The first approach to this task was to identify VA's most prevalent patient care problems. These were categorized as "Special Emphasis Areas," which were announced in a 1977 Research and Development Letter to the field[15] specifically inviting cooperative studies in these areas.

High Priority Research Programs

In addition to encouraging research in these Special Emphasis Areas, a few "High Priority Areas" were selected for preferential funding. These High Priority Areas were intentionally narrow and never consumed a large part of the budget, to avoid depleting the general funds supporting the Merit Review program. During the late 1970s, High Priority programs were begun in aging, the biology of alcoholism, the biology of schizophrenia and tissue regeneration.

In defining its original High Priority Areas, VA deliberately stayed away from topics heavily emphasized by other agencies. Even though VA had large numbers of patients with cancer and heart disease, these areas of research were well-funded by the NIH, so that a small, directed initiative by VA did not seem appropriate.

Aging

The High Priority Area in aging was already in place, as research in the Geriatric Research Education and Clinical Centers (GRECCs) was receiving preferential funding. The original GRECC program, spearheaded by Paul Haber, M.D., while he was ACMD for Extended Care, had been passed into law and funded, together with money to pay the salaries of research staff within the GRECCs. But the research staff needed support to carry out their research. The original GRECC units were "tooling up" when the author arrived in VA Central Office in 1974, and Haber lobbied hard to have her provide earmarked research support. The Medical Research leadership, however, insisted that these new programs be peer reviewed. A compromise was reached: GRECC research projects were required to undergo Merit Review, but those approved would be fully funded even if other research budgets were being cut. This arrangement lasted into the 1980s, when budget constraints made its continuance impractical. By that time, research in the GRECCs had been well established.

The GRECCs, in their educational effort, sponsored Geriatric Fellowships for clinicians wanting to specialize in this area. In 1980, as a part of the Aging High Priority program, Medical Research Service offered a one-year research extension of these fellowships, handled within the Associate Investigator program.[16]

Aging research outside of the GRECCs, quantitatively much greater than that within the GRECCs, was considered to be in a Special Emphasis Area but received no budgetary preference.

New High Priority Areas: Alcoholism, Schizophrenia and Tissue Regeneration

VA patient demographics guided the choice of the next two High Priority Areas. Alcoholism and its related diseases caused the most VA hospital admissions. Schizophrenia was clearly responsible for the largest number of patients occupying beds in the VA medical system at any given time. To leverage the existing strengths of VA research without duplicating research being done elsewhere, the biology of these conditions was selected for focused VA programs.

To coordinate the High Priority programs from the Central Office, Robert Allen, Ph.D., was recruited from the NIH. He organized conferences and meetings, took charge of tracking all the defined High Priority Areas to assure their protected budget lines, and interacted with the individuals in the programs. Allen became the glue holding these programs together, and kept them pointed toward their goals.

Figure 16.19. Matthew Kinnard, Ph.D., Chief of Field Operations, and Robert Allen, Ph.D.

Alcoholism

David Rutstein, M.D., at that time a VA Distinguished Physician in Boston, visited Newcomb in 1977 and urged that VA follow up on recent interesting studies on the familial incidence of alcoholism. Stimulated by Rutstein's enthusiasm, CMD Chase held a meeting attended by Sir Hans Krebs (who was interested in the biology of alcohol and friend of Paul Srere, Ph.D., from Dallas), Rutstein, Srere and a number of other VA scientists, along with a sprinkling of Central Office staff. One outcome of this meeting was a conference on the biology of alcoholism held in Florida in January 1978. The consensus was that the greatest need was to recruit competent scientists from other areas into the area of alcoholism.

Marcus Rothschild, M.D., Chief of Nuclear Medicine at the Manhattan VA and a Middleton Award winner for his research on the liver, was interested in this problem. He agreed to spend three months in Central Office, where he started a program of "Alcoholism Scholars": scientists with M.D. or Ph.D. degrees who were not currently working for VA were invited to present applications for three-year fellowships to work in a VA laboratory on the biology of alcoholism. This program received 85 applicants in its first review cycle. Rothschild formed a special committee to review the applications, and 13 Alcoholism Scholars were chosen.

The following year, VA scientists as well as non-VA scientists were permitted to apply, and six more Alcoholism Scholars were selected from 60 applicants.

These Alcoholism Scholars (Appendix IX), most quite young, were treated as an elite corps. They received their appointment certificates in ceremonies attended by the VA Administrator and Chief Medical Director. They were brought together to share their research experiences. Of the 13 Scholars in the first round, all recruited from outside VA for this program, nine continued with VA careers after their appointments expired.

Figure 16.20. Marcus Rothschild, M.D.

A third round in this effort, known as the "Innovative Alcoholism" program, was directed to innovative proposals from VA laboratories. Announcement of this program aroused much interest from VA researchers who were not primarily in the field of alcoholism research and generated 97 letters of intent, followed by 63 full proposals. After review by special committees in June 1981, 11 projects were selected as both innovative and highly meritorious. Owing to a budget shortfall, their funding was postponed until October 1982.

A task group reviewed the program in early 1982 and recommended that the VA alcohol research program be expanded to include clinical research combining the basic work under way with studies incorporating VA's large patient care effort in this area. In response, the Medical Research Service announced a competition for Clinical Research Centers in Alcoholism. After extensive review, the first such Center was awarded to San Diego VA Medical Center, with Mark Schukit, M.D., one of the original Alcoholism Scholars, as its Chief.

Schizophrenia

Claude Baxter, Ph.D., from the Sepulveda (Calif.) VA Medical Center, spent six months in Central Office to launch the High Priority research program in schizophrenia. Baxter, a neurochemist well known for his work with GABA in the brain, reviewed the literature on the biology of schizophrenia, which he found to be extensive and complex. He then identified the experts in the field, both within VA and from universities in the United States and abroad. Many of these scholars were invited to a conference held in Harper's Ferry, W.Va., in April 1979, where they presented formal papers, subsequently edited in a *Proceedings* volume.[17] This meeting reviewed the state of the art in research on the biology of schizophrenia. The

participants also considered how VA could best launch a focused attack on the problem. The conference consensus was that VA should establish Centers of Excellence in the biology of schizophrenia, initially directed toward improving classification of the various types of schizophrenia as a necessary requisite to meaningful biologic approaches to addressing the disease.

Figure 16.21. Attendees at the Harper's Ferry meeting on schizophrenia research, 1979. First row: C.E. Beck, E.D. Bird, Hiatt, Betty Uzman, Robert Allen, Aaron Janowski, A.L. Goldstein, Joseph Zubin. Second row: Phillip May, J.E. Kleinman, Sheri Buchsbaum, Monte Buchsbaum. Third row: Earl Freed, W.T. Carpenter, Jr., Robert Savage, Theodore P. Zahn, Jack Ewalt, J.R. Perez-Polo, D.R. Weinberger, F.A. Henn, Arthur Yuweiler, T. Melnechuk, Philip Berger, Joseph Collins, W.A. Brown, N.R. Schoolar, H.A. Nazrallah, J.O. Cole, J.A. Gfeller, D.H. Ingvar, T.M. Itil, J.W. Mason, Claude Baxter, Loren Mosher, Marguerite Hays, J.M. Davis, R.T. Canoso, M.M. Singh.

Proposals for Schizophrenia Biologic Research Centers (SBRCs) were formally solicited in September 1979.[18] Nineteen medical centers sent letters of interest, seven were invited to submit full applications, and six did so. The Bronx VA Medical Center was chosen for funding of an SBRC, with Kenneth L. Davis, M.D., as its Chief, and funding began in January 1981. During 1981, after another competition, a second SBRC was selected at the Palo Alto VA Medical Center. Staff in both of these SBRCs published widely on schizophrenia and other mental illnesses, but the original goal of biologically based classification proved elusive.

Regeneration

VA Administrator Max Cleland, a Vietnam Veteran who had lost both legs and one arm in a grenade explosion, was interested in the prospects of limb regeneration. VA defined "tissue regeneration" as a High Priority research area. Vernon Nickel, M.D., Director of the Rehabilitation Engineering Research and Development Service (Chapter 20), together with Robert O. Becker, M.D., Middleton Award-winning orthopedic surgeon at the Syracuse (N.Y.) VA Medical Center, organized a conference on "The Mechanisms of Growth Control." Becker was a pioneer in this area, having studied the effects of electrical stimulation on bone growth and repair. The conference, held Sept. 26–28, 1979, was widely attended by scientists

and others interested in tissue regeneration from all over the United States and from Russia, Japan and Canada.

The Paralyzed Veterans of America service organization was strongly supportive of research in the area of spinal cord regeneration. At the same time, basic neurobiology studies, many being carried out within the VA research program, suggested that such regeneration might no longer be in the realm of science fiction. Betty Uzman, whose scientific specialty was neurobiology and who knew most of the principal players in the area of nerve regeneration, assumed responsibility for the regeneration High Priority Area.[19]

The formal VA regeneration program began taking form in 1980, when Dr. Uzman chaired a planning committee that met in Palo Alto, Calif., and recommended that VA establish an Office of Regeneration Research. A competition ensued for this office, which was established at the Portland (Ore.) VA Medical Center in early 1981, with Frederick Seil, M.D., a neurologist with an active research program in nerve regeneration, as its Chief.[20] During the 1980s and 1990s, this Office coordinated regeneration research in VA, defined which VA research projects fit into the High Priority concept for preferential funding, published a newsletter, and later established a training program in regeneration research. Through Dr. Seil and his office, VA held biennial conferences on regeneration research that were well attended and encouraged collaborations in the field. Most of the effort was in the area of neural regeneration, work supported in collaboration with the Paralyzed Veterans of America and the VA Rehabilitation Research Service, as well as Medical Research Service.

How useful was the concept of High Priority programs?

Although the amount of extra funds earmarked for these high-priority programs was relatively small, the programs proved productive. In addition to their scientific contributions, they helped to satisfy some of the special interest groups that wanted to divert VA resources to areas of their particular concern.

Tissue regeneration

The conferences, newsletter and personal encouragement from the Office of Regeneration Research supported expansion of VA research in this field and led to some early successes in regeneration in the central nervous system.

One of the leaders in this field is Stephen Waxman, M.D., Ph.D., who was a part of the original planning group for this initiative. Dr. Waxman was Chief of Neurology at the Palo Alto VA Medical Center until 1985, when he became Chair of Neurology at Yale. The Eastern Paralyzed Veterans of America donated a Neuroscience Research Center on the West Haven (Conn.) VA campus to house the joint VA-Yale program of regeneration research under Dr. Waxman's leadership. Beginning while in Palo Alto, Waxman's laboratory studied the South American knife fish, *Sternarchus*, which has the ability to regenerate the spinal cord in its tail when the tail is bitten off by a predator. This process was studied in the laboratory in normal and tail-amputated *Sternarchus*, using anatomic, electron microscopic and cell culture studies. The source of the regeneration was identified as the ependymal cells of the

center of the spinal cord. This seminal work has been expanded in other laboratories to produce some nerve regeneration in certain mammals. While still a long leap to regeneration of cells in a human's severed spinal cord, the objective is no longer considered hopeless.[21, 22]

Schizophrenia

The Bronx Schizophrenia Biologic Research Center remains active. The VA program is now fully integrated with that of the Mount Sinai School of Medicine and is the location of a large group of researchers in biologic psychiatry. One of its most important findings has been the correlation of homovanillic acid with schizophrenic symptoms. The group has been studying the genetics of schizophrenia and, through a gene bank, has established pedigrees of schizophrenic families. A bank of brains donated by deceased schizophrenia patients led to the finding that schizophrenic brains are depleted of dopamine. The group has also studied Alzheimer's disease, devised scales for its assessment, and developed tacrine, the first drug approved by the Food and Drug Administration to combat the disease.[23]

Biology of alcoholism

The 19 Alcoholism Scholars appointed in 1979 and 1980 (Appendix IX) were still publishing scholarly papers as of a 2002 review, and 15 (87 percent) were conducting research on the biology of alcoholism.

Marc Schukit, M.D., of the original group of Scholars, has won many awards for his genetic studies of alcoholism. His laboratory tried to identify the specific genes involved in alcoholism. He described the significance of his most important findings as a key to formulating a theory that alcoholism's genetic causes are heterogeneous; selecting a particular marker of risk, showing that the marker, a low level of response to alcohol, related to a family history of alcoholism and predicted alcoholism 15 years later. He and his colleagues had studied a group of 453 subjects and were in the process, in 2002, of studying their 444 offspring. Schukit commented, "I also hope that some of my work in comorbid psychiatric disorders in the context of alcohol and drug dependence has been useful to the field."[24]

Boris Tabakoff, Ph.D., who spent 1984 to1990 in high positions at the National Institute on Alcohol Abuse and Alcoholism (NIAAA), was, in 2002, chair of the Department of Pharmacology at the University of Colorado, where he was studying the cellular effects of alcohol. Tabakoff said:

> "I believe that we were the first to link brain vasopressin and vasopressin-like peptides to the development of tolerance to alcohol. We described different forms of alcohol tolerance (those that involved learning and conditioning and those that did not involve components of learning). We demonstrated that one could, with manipulation of brain vasopressin peptides and modulation of brain noradrenergic systems, control the learned forms of tolerance, while leaving the other components of tolerance intact."

Tabakoff also demonstrated the involvement of the NMDA (N-methyl-D-aspartate) glutamatergic systems in the acute and chronic effects of ethanol with initial results that

showed that ethanol was significantly and potently inhibiting NMDA receptor function. He noted that:

> "My ideas were then extended to encompass the chronic effects of ethanol. These results substantiated that the NMDA receptor system responds (adapts) to ethanol administration by an upregulation of receptor number and receptor function."

Tabakoff extensively studied the effects of ethanol on the dopamine receptor-stimulated adenyl cyclase activity. He said:

> "The work continued with demonstrations of the chronic effects of ethanol, and the adenylyl cyclase systems and the observation that human alcoholic subjects had lower platelet adenylyl cyclase activity compared to controls. This clinical study was done while I was at the Westside VA in Chicago.
>
> "More currently, in the adenylyl cyclase area, we have created transgenic animals and null mutant mice, as well as utilizing selective breeding techniques and QTL analysis which all point to the role that adenylyl cyclase plays in the etiology of alcohol tolerance and dependence."[25]

Carrie Randall, Ph.D., who was recruited into the Alcoholism Scholars program at the Charleston (S.C.) VA Medical Center, received the Distinguished Alcohol Research Award from the Research Society on Alcoholism in 1998 and the Keller Award from NIAAA in 2000. She stated that the VA Alcoholism Scholar award allowed her to "build an independent research program from the ground up." She remained in VA for 14 years, until she was recruited to the State University of South Carolina. Randall studied the role of prostaglandins in the etiology of Fetal Alcohol Syndrome and was, in 2002, studying the relationship between social anxiety and the use/misuse of alcohol.[26]

Adron Harris, Ph.D.'s work focused on the study of drug addiction with emphasis on alcoholism. He clarified several molecular targets of alcohol action in the brain and studied actions of ethanol on GABA receptors.[27]

Raj Laksman, Ph.D., at the Washington (D.C.) VA Medical Center made significant contributions in the field of alcoholic hyperlipidemia. He found that the condition is partly due to the formation of abnormal triglyceride-rich remnant particles that are defectively cleared by the liver.[28]

Anna Taylor, Ph.D., of the Brentwood (Calif.) VA Medical Center and UCLA, focused her research on the neurobiology of alcoholism. She was among the first to demonstrate that prenatal exposure to ethanol produces a consistent pattern of enhanced neuroendocrine and behavioral responses to stress and psychoactive drugs, including ethanol, in adult fetal alcohol-exposed offspring. Recognizing that alcohol affects neural and endocrine systems that are intimately involved in immunological responses, her team of investigators demonstrated adverse effects of alcohol on immune competence following prenatal as well as adult exposure.[29]

Ladislav Volicer, M.D., Ph.D., is one of the Alcohol Scholars who later moved into a different field, but one also of great importance to VA. He continued his basic neuropharmacological research and also initiated some clinical studies looking at factors influencing genetic predisposition to alcoholism. Volicer became the medical director of a Dementia Special Care Unit at the GRECC in Bedford, Mass., and developed a palliative care program for patients with advanced dementia. This program, which was described in *JAMA*,[30] was among the first to consider advanced dementia a terminal disease.

John Crabbe, Ph.D., of the Portland (Ore.) VA Medical Center was an early proponent of genetic animal models and provided insight about the relationships among the different behavioral components of the overall alcoholic syndrome. For example, he contributed to our understanding that alcohol consumption and severity of alcohol withdrawal are negatively genetically coupled in rodents.[31]

These leaders are among many who helped the High Priority programs started in the late 1970s to serve VA and its patients so well. One of the advantages of a relatively small, in-house research program like the VA Medical Research program was found in its administrative flexibility; all that was necessary to start these programs was an initial decision to proceed, recruitment of the staff and expertise needed, and money set aside. Later, when it seemed to those in charge that these programs were no longer necessary, they could be abandoned in favor of other new initiatives.

References

1. Telephone interview with Laurence Foye, M.D., March 12, 1988.

2. Foye, L.V., Jr., M.D., "10-77-219 Circular. FY 1977 VA R&D Information Systems (RDIS)." September 23, 1977.

3. Newcomb, T.F., M.D., "IL 15-74-12 R&D Letter. VA-NIH Review Feasibility Study." June 4, 1974.

4. Interview with Howard Berman, May 1, 1992 at Mr. Berman's office in the Westbard Building of NIH.

5. Interview with Thomas Newcomb, M.D., March 29, 1992 at a hotel lobby in Washington, DC.

6. Jacoby, W.J., Jr., M.D., "10-80-34 Circular. Merit Review Appeal Process." February 19, 1980.

7. Foye, L.V., Jr., M.D., "10-77-61 Circular. PhD Scientist Appointments in Medical Research (Program 821)." March 15, 1977.

8. Foye, L.V., Jr., M.D., "10-77-60 Circular. Research Career Scientist." March 14, 1977.

9. Foye, L.V., Jr., M.D., "10-75-277 DM&S Circular. Special pay for physicians and dentists." November 12, 1975.

10. Newcomb, T.F., M.D., "IL 15-75-5 R&D Letter. Medical Research Service Career Development Program." July 30, 1975.

11. Newcomb, T.F., M.D., "IL 15-77-16 R&D Letter. R&D Career Development Program." November 18, 1977.

12. Thomas, D. "Data base of information about Career Development appointees." 1989.

13. Interview with William H. Oldendorf, M.D., November 5, 1991 at Dr. Oldendorf's office at Brentwood VA Medical Center.

14. Newcomb, T.F., M.D., "10-76-177 Circular. R&D Priority Assessment." August 17, 1976.

15. Newcomb, T.F., M.D., "IL 15-77-8 R&D Letter. Planning and Development of Cooperative Studies in Special Emphasis Areas." June 24, 1977.

16. Jacoby, W.J., Jr., M.D., "10-80-186 Circular. Opportunity of research training for geriatric fellows." August 29, 1980.

17. *Perspectives in Schizophrenia Research*. Baxter, C.F. and Melnechuk, T., eds.; New York, NY: Raven Press, 1980.

18. Hays, M.T., M.D., "IL 15-79-11 R&D Letter. Solicitation of Letters of Intent for Schizophrenia Biologic Research Centers." September 5, 1979.

19. Uzman, B.G., M.D., "A report on progress in research High Priority Areas." *Newsletter: Research and Development in Health Care*, Washington, DC, December, 1979. 7.

20. Hays, M.T., M.D., "IL 15-80-4 R&D Letter. VA Regeneration Research." May 21, 1980.

21. Anderson, M.J. and Waxman, S.G., "Neurogenesis in adult vertebrate spinal cord in situ and in vitro: a new model system." *Ann NY Acad Sci*, 1985: 213-233.

22. *Form and Function of the Brain and Spinal Cord*. Waxman, S.G., ed. Cambridge, MA: MIT Press, 2001, 231-233.

23. Interview with Kenneth Davis, M.D., November 9, 1993 at Washington, DC hotel lobby.

24. Letter from Marc Schuckit, M.D. to author, written at San Diego, CA, March 18, 2002.

25. Letter from Boris Tabakoff, Ph.D. to author, written at Denver, CO, April 1, 2002.

26. Letter from Carrie Randall, Ph.D. to author, written at Charleston, SC, May 10, 2002.

27. Letter from Adron Harris, Ph.D. to author, written at Austin, TX, April 28, 2002 (Email).

28. Letter from Raj Lakshman, Ph.D. to author, written at Washington, DC, April 19, 2002.

29. Letter from Anna Taylor, Ph.D. to author, written at Los Angeles, CA, July 9, 2002.

30. Letter from Vladislav Volicer, M.D., Ph.D. to author, written at Bedford, MA, May 10, 2002.

31. Letter from John Crabbe, Ph.D. to author, written at Portland, OR, March 14, 2002.

Chapter 17. Meeting Funding Challenges: "Project Scissors"

In November of 1977, VA's medical research program encountered a crisis, as pressures to restrict federal budgets and growing demand for research funding collided in a way that sent shock waves through the community of investigators, VA research managers, hospital administrators and medical school affiliates.

The immediate, precipitating factor was arrival at VA of the President's budget for fiscal year 1979, which proposed a cut in the Medical Research budget to well below current (fiscal year 1978) operating dollars. The Research Service believed that most of the "fat" had already been cut out of the program and that it would be impossible to operate under the proposed budget with a "business as usual" approach. Something more drastic would be necessary; aggressive reductions would have to be made, in an effort that would become informally known as "Project Scissors".

Although the President's budget does not represent final funding decisions (the actual budget is ultimately determined by Congressional appropriation, a lengthy process worked out over several months), VA was obliged to prepare to operate at the proposed, lower level. Before the actual budget figure for the next fiscal year would be known, several developments would take place:

- The research program's national leaders thoroughly explored cost-cutting options, and formulated a new policy that would eliminate or curtail research funding at locations that appeared unproductive;
- Criteria were established to weigh relative productivity of research, such as instances of findings being published;
- An unprecedented series of nearly three-score site visits by small teams of researchers and administrators were made to evaluate ongoing projects;
- An ad hoc national "caucus" took place, at which investigators and administrators from throughout the system expressed concerns, debated solutions and ultimately reached a level of consensus on the logic and fairness of the evolving funding process; and
- A new method of supporting research at facilities with small research programs was established, in the form of two regional research and development offices.

The problem had been brewing for some time, as a cost-conscious period in federal budgeting had led to three years of relatively "straight line" funding for VA's medical research program. At the same time, VA was recruiting many excellent physician-scientists, willing and able to do needed research. To deal with these pressures, VA had already increased peer review and, on advice of the Merit Review Boards, gradually phased out programs. This was a painful process, as VA research is an intramural program and the people losing funding were VA's own employees. The cuts clearly triggered reassignments, resignations and retirements.

The Medical Research Service was supporting research programs in 123 VA medical centers with a total annual budget of $123 million. Ninety percent of the support was concentrated in 56 medical centers with large research enterprises. The other medical centers conducting research fell into several categories. In some cases, research support had started at modest levels when the medical center participated in a cooperative study or was given another special assignment. When that purpose was fulfilled, some of the "core" support remained and often paid for the salaries of one or

two employees. In other cases, especially those distant from a medical school, one or two individuals consistently carried out high-quality research; they continued to be productive and received Merit Review Board approval despite their isolation. The monies sent to those distant medical centers supported the productive investigators and included additional "core support" for local research administration. There also were situations where a highly affiliated hospital, with academically qualified physicians, was small enough that the justifiable number of research physicians was small. And then there were situations of an emerging program on its way up, or a declining program on its way down.

Despite changes over the preceding decade, administration of research money remained highly decentralized. The medical center's Research and Development Committee had much of the responsibility for deciding how to best use the money sent. As for review from Central Office, larger projects underwent individual Merit Review and the research of newly recruited investigators was reviewed by the Research Advisory Groups (RAG). Site-visit teams had been reviewing the overall research programs at medical centers with medium and large research budgets. Except for occasional Central Office staff member administrative site visits, medical centers with total budgets below $550,000 per year had not ordinarily been visited. Central Office staff often were not familiar with how these smaller research programs were using their money.

Medical Research Service staff wanted to protect the two most highly regarded programs, the Research Career Development and Cooperative Studies Programs. Both had been maintained at constant budgets during the recent budget squeeze.

VA's medical research budget had grown steadily during the 1950s and 1960s but had leveled off after fiscal year 1975 (Figure 16.5 in Chapter 16). At the same time, the program, which received congressional attention in earlier days, was now relatively "invisible." While the Department of Medicine and Surgery and the Administrator's Office spoke of the importance of the program, they did not seek increased budgets. Research received relatively little attention in VA's congressional hearings. Despite all the publicity and recognition that had been generated on Capitol Hill, and even despite the 1977 Nobel Prizes won by VA scientists Rosalyn Yalow and Andrew Schally, the picture had not changed.

Settling on a plan

After they learned of the proposed FY 1979 budget cut, the Medical Research Service staff evaluated three potential responses:

1. A year of "no new initiatives." With this plan, VA would not start any programs in new high-priority research areas, would not start research where it didn't already exist (including in newly constructed hospitals), and would not support new affiliations or newly recruited staff.
2. Redirect funds by a variety of budgetary manipulations, including restricting dollar support for any individual investigator or any medical center. Some advisors felt they should cut off funds of part-time VA staff. Others recommended a retroactive application of a merit review "pay line." All these options involved reneging on a commitment made after peer review approval of the research's scientific merit. All but the merit review pay line, the Medical Research Service staff believed, would undercut the research of some of VA's best

investigators.

3. The third approach, which earned the sobriquet "Project Scissors," was to entirely cut off funding from medical centers with marginal programs. The rationale was that a research program needs a "critical mass" of scientists to maintain quality. The National Research Council of the National Academy of Sciences, in its1976 report *Biomedical Research in The Veterans Administration*, had recommended withdrawing research support from hospitals not affiliated with medical schools. Other advisors agreed with this approach. Review of funding patterns showed that, with few exceptions, hospitals with small research programs put proportionally more support into common resources and into projects that had been approved only locally, with less support provided for Merit Review-approved research.

Of the three options considered, cutting off smaller programs involved the fewest Merit Review-approved programs and was the approach chosen. Many medical centers would be affected. Depending on which were finally identified, approximately 55 with the smallest research budgets would need to be cut to save the necessary monies. In response to advice from the Research Advisory Committee, Medical Research Service also decided to place a $100,000 limit on VA support of any investigator's program.

The author was prominently involved in these deliberations and actions, having been Director of VA Medical Research for more than three years. Thomas Newcomb, M.D., the ACMD/R&D, worked closely with the author in evaluating options and agreed on this approach. It next needed to be discussed with those higher in the VA administration. Newcomb asked the author to present the plan to Dr. Chase, the Chief Medical Director and Dr. Thomas Fitzgerald, the Deputy in charge of medical center operations. The three discussed the adverse effects expected from each cost-cutting measure. Chase asked the author for her recommendation. She proposed cutting the small programs and offered to exercise care. She also recommended placing a $100,000 limit on the large individual programs, reasoning that these programs could remain viable and probably find other support. Chase agreed and said he would bring the matter to Administrator Cleland's attention, cautioning that they could not talk publicly about the budget until after the President's budget message of January 23, 1978.

Choosing the "Scissors" medical centers

To identify which medical centers' research programs to cut, the Medical Research Service staff decided that except for a few places with so little research support that they could persuade their management to accept an administrative decision, they would first visit the targeted sites.

The 75 medical centers with the least research funding were the likely candidates. The BECC staff at the Sepulveda (Calif.) VA Medical Center, which handled the R&D Information System, coded and retrieved information about the abstracts, papers and books published by research investigators at these 75 medical centers. For balance, information was gathered about the three centers with the most research money. They decided to site-visit all but one of the medical centers on the list that received total funds of less than $300,000. The exception, a medical center with only $150,000, had produced so many publications in prestigious journals that they eliminated it from the "at risk" list. In the group with funding between $300,000 and $550,000, the decision to visit was made primarily on the basis of an index of medical journal publications used to score work being done at each

location. After an analysis of the index, 11 medical centers, 10 of them with research funding over $300,000 per year, escaped further review.

Eight medical centers with research funding under $12,000 per year were "zeroed out" after the author called the Medical Center Director to discuss the situation. The Director of a ninth medical center that had received only $936 that year persuaded the author to make a site visit because of their pending medical school affiliation.

The 58 medical centers to be site-visited included all the others with research funding below $150,000, 16 of the 17 with funding between $150,000 and $300,000, and 7 of 17 with research funding between $300,000 and $550,000.

The site visit teams

Twelve teams of site visitors were selected—each with two members, an Associate Chief of Staff for Research and Development (ACOS/R&D) from a VA medical center and a VA clinician-scientist. All site visitors had Merit Review funding of their own research. Generally, one team member was from a medical center with a large research program and one from a modest program. Each site visitor made three to five visits, some with one partner and others with another partner.

Site visitors were recruited by telephone. They were asked to commit time during late January and early February and also to attend a meeting in Central Office Feb. 22 and 23, 1978. The embargo on budget information prevented any of them from knowing the purpose of their visits.

By Christmas, all site visitors had received information about their partners and which hospitals they would visit. Medical Research Service had formally requested permission for their participation from their medical center directors and had also notified those programs that would be site-visited, telling them when the visit would be and who would be visiting. They could not, of course, be told *why* they were being visited. During January, materials for site visitors were compiled. The BECC group at Sepulveda assembled packets showing each hospital's funding pattern for the past four years and listing all investigators with their funding histories, roles in the medical center, salary source, publication histories and the amount of time they reported spending on research. These information packets were sent to the medical centers for verification and updating. The updated information was ready for the site visitors when they arrived. A site visitors' questionnaire was developed to help them make succinct evaluations.

Announcing "Project Scissors"

In early January, other persons in Central Office were notified about these plans, including the list of the medical centers to be site-visited between Jan. 23 and Feb. 20. Representatives of the other major offices in the Department of Medicine and Surgery were invited to the Feb. 22-23 meeting.

On Jan. 23,1978, President Carter announced his budget plan to Congress. That morning, the author read this message on a conference call to all the research programs:

> "As you may know, today is the day that President Carter announces his Fiscal Year 1979

budgetary recommendations to the Congress. This budget has been prepared by the Office of Management and Budget after considering the needs of all parts of the executive branch of the government. The President's budget request for Fiscal Year 1979 will impose a severe constraint on the medical research budget. This means that drastic action has become necessary. A number of options are possible, and they have been discussed, not only within R&D but with the Chief Medical Director and the Administrator.

"Two decisions have been made. The first is that, with but a few exceptions in high priority research areas, we will place a $100,000 ceiling on the funding of programs of individual investigators. The second, more far-reaching decision is to terminate medical research funding in many health-care facilities. In a few cases, I have already talked to the Directors of the facilities and informed them that no FY 1979 funds will be sent. The other facilities are still in process of being identified.

"Site visits to selected hospitals will occur during the next month. The visitors are being asked to assemble as strong a case as they can for maintaining medical research funding at the hospitals they visit. I'm sure that those of you who are being visited will help them to do this. On February 22 and 23, there will be a meeting here in Washington at which the site visitors will present their findings. As a result of this meeting, we will assemble a listing of the facilities, ranking them according to our best assessment of the relative importance of maintaining the medical research program.

"As things look now, basic institutional medical research funding will have to be terminated in the majority of the facilities being site-visited. This is a process that will be very painful. We would like to assist investigators at the facilities where funding is to be discontinued who have high priority merit review approvals, and who wish to do so, to transfer to facilities with continuing programs. If those of you who are not being site-visited during the next month, and hence who are not in jeopardy of losing your medical research programs, will inform us of your staffing needs, we may be able to help you locate some fine investigators.

"In addition to this stricture on our operating budget, the current FY 1979 construction budget contains no major or minor research construction.

"There is still hope, of course, that the final budget allocation from the Congress will make this entire effort needless. I sincerely hope that, in the end, it turns out to have been a waste of time and effort. But we have no real reason to believe that this hope has any basis. We have, therefore, no choice but to proceed on the assumption that the current budget is to be the final budget."

The announcement left people stunned. While many site visitors had suspected something like this was in the wind, others were shocked to be involved in such an unpleasant process. People at the affected medical centers were understandably upset.

Medical Research Service prepared a letter to site visitors, for distribution coinciding with the President's budget announcement, explaining what was going on and containing a suggested agenda. If the program was affiliated, they were asked to visit the medical school or to talk to its

representatives. They were expected to meet with the Research and Development Committee to review their procedures and attitudes and to try to interview all of the research investigators. Site visitors were asked to orient their visits to the positive. They were to serve, in the late February meeting, as advocates for medical centers they had visited. Obviously, salient negative aspects should be included. However, their primary role was to present reasons the program *should* be continued, rather than the opposite.

The next month was one of frantic activity. A number of site visitors became so upset by the turmoil their visits caused at medical centers that they protested.

The caucus

By the Feb. 22-23 meeting, emotions among site visitors had reached a high pitch. One ACOS/R&D devised a plan by which site visitors would agree to vote unanimously a top score to all programs reviewed. This would, in effect, eliminate the possibility of using site visit results. He decided to drop this approach when another ACOS organized a Feb. 21 caucus of site visitors to consider a joint stand. He proposed that the caucus consider stating that:

> "1. The site visitors are unwilling and unable to advise Research Service in Central Office about which individual hospitals should have their research programs completely eliminated.
> 2. The administrative officers in Central Office Research Service who have decided on this policy should implement it themselves without help.
> 3. They should evaluate the adverse effects of this implementation.
> 4. The caucus members understand that other alternative policies might well result in significant restrictions of funds to their own institutions."

This caucus met as planned and later asked the author to join the meeting for her response to the sentiments expressed by the group. She explained that all were hoping that none of the process would prove necessary, as work was being done on a number of fronts to try to influence Congress to increase the budget. However, it was necessary to prepare for the possibility of no increase. She explained that their descriptive input was critical to the meeting, but that their votes, while helpful, were not essential. She again asked them to present all of the arguments they could muster in favor of retaining research at each of the medical centers they represented.

The group agreed jointly to vote a simple yes-no question. For each medical center, each attendee would vote that the program be retained or discontinued. If all site visitors wanted to vote for continuing all programs, their input would nevertheless be useful to other attendees in making decisions. The author pointed out that, in their presentations, the comment that "I would gladly give up money from my own program to retain this program" would indeed be a strong argument. After considerable discussion, this approach was accepted. The author agreed to put the caucus resolutions on the agenda first thing in the morning.

The meeting

The next days' meetings were attended by 95 persons: site visitors, representatives from other parts of Central Office and most VA Medical Research field advisors. Each was given information about

the medical centers to be reviewed and asked to vote either to retain or discontinue each program. The medical centers were reviewed in groups relatively comparable to each other, eight or nine in a group. For each medical center, the site visit team leader and partner described their visit. At the end of each group of presentations, the assemblage reviewed the medical centers in the group and made an effort to rate them against each other. Attendees rated the medical centers as they heard about them, and also reviewed their ratings at the end of the second afternoon in light of what they had heard about the entire group. The site visitors were true to their task of presenting the positive side, but in some cases it became apparent that some research money was indeed being wasted. As time went on, site visitors and other attendees began to work from the same viewpoint.

By the end of the second day, a consensus had emerged about a number of issues:

- Even at medical centers with the smallest programs and a fair degree of mediocrity, there were occasional bright lights. Individual scientists managed to carry out excellent research despite lack of a supportive environment. There was general consensus that these persons should be allowed to continue.
- Frequently, money allocated outside of peer review, for administrative support and small projects, was not being used well.
- Smaller research programs would benefit from outside support of the type provided by the university in closely affiliated medical centers. The group considered pairing smaller centers with stronger ones.

Also by the end of the second day, a proposal emerged that VA set up Regional Offices to administer smaller research programs. These offices would take over administrative chores now being done at each medical center. Administrative monetary support would be given to the Regional Offices to support the assigned research programs, rather than directly to the medical centers. The Regional Offices would also provide scientific support and "know-how" for their research programs.

Waiting

Over the next few months, the threatened program cutoffs received considerable attention. The impact was brought up in congressional hearings, stimulating specific research program hearings by the Senate Veterans Affairs Committee. Medical Research Service was invited to defend its position in meetings with a number of members of Congress. Contacts with Senators and Representatives were coming from many of the affected medical centers and Cleland was being pressured to have the White House reconsider VA's research budget.

The next months were anxious times for the medical centers at risk as they waited for final resolution of the budget in Congress. It was not until almost the beginning of the next fiscal year that the final budget was signed containing a $10 million increase for Medical Research. As a result, it was possible to continue medical research funding at all of the medical centers that had been visited.

One year later

Toward the end of fiscal year 1979, the author wrote to the visited medical centers, requesting feedback about the effects of the review process. Research at 49 of the site-visited medical centers had now come under the jurisdiction one of two new Regional Offices—one at Livermore, Calif., with Werner Schlapfer, Ph.D., as Chief, and the other at Perry Point, Md., with William Pare, Ph.D., as Chief. As a result, these medical centers had little or no local discretionary research monies. On the other hand, the Chiefs of the Regional R&D Offices had, by this time, visited them all. Responses about the Regional Offices ranged from "it is another level of bureaucracy" and "the loss of our autonomy is bad" to "it is our only source of hope" and "it was the major positive effect of the process."

One of the medical centers, which subsequently showed an increase in both funding and activity, complained of the enormous amount of time required for preparation for the site visit. But their outcome was generally positive, as the research program had received significant support from top hospital management, substantive support from its affiliated university, input from the Veterans' organizations, and strong support from their members of Congress. The director of one hospital with a small research program, which had decided to close out research entirely, said the site visit had helped them realize that they were not an appropriate site for a research program.

Another medical center, which reported decreases in funding and activity since the site visit, said that their program was in serious difficulty now and had lost five people. They said that the top hospital administration had assumed that their program would be discontinued and the affiliation was in jeopardy. On the other hand, a comparable hospital in the same funding range reported increased activity. Their medical school and community support had increased, and they had made the decision to push their affiliation. Another medical center that had increased its research activity since the visit described the severe negative effect on local morale, despite having received a great deal of support from medical center management, the affiliated school, the community and members of Congress.

With regard to the site visit process itself, a number of hospital officials wrote that it had been helpful and had improved communications with Central Office.

Many, however, complained of the long period of uncertainty, and pointed out that a written game plan would have been helpful. They described the drain on the time of the ACOSs seeking personnel replacements. "We cannot over-emphasize the negative effect resulting from ambiguous communications from Central Office. Obviously the whole system would work better if Central Office provided continuous encouragement rather than continued threat of withdrawal of financial support." And, "The period of time between notification of the site visit and receipt of fiscal year 1979 budget information was fraught with uncertainty, dampening of research activities and resigning of research staff."

The individual impact on members of the research program included personal stress and discouragement. Some continued to feel pessimistic despite the restoration of their funds. There was resentment about the threat that small programs were to be cannibalized by the large, well-organized, well-staffed and well-funded research centers. Some responders said that it was now

hard to interest physicians in research and that the enthusiasm among clinicians to engage in relatively minor direct care-related projects had been dampened. "There's a feeling among the clinical staff . . . that VACO is unsympathetic to their commitment to VA and the contributions they have made to this hospital." On the other hand, another hospital reported that the process had increased the support for research by the patient care elements. They have "closed the ranks between various professions and focused attention on the need for research." Another hospital said, "Many individuals involved in patient care, but only peripherally concerned with research, expressed great dismay about possible loss of the research program and felt they could not remain affiliated with a VA Medical Center where research was not done."

Other hospitals reported that "to the extent that the department chairmen, dean, and faculty of the school were unified in their support of the research program, the site visit was beneficial in making school officials recognize the critical need for research support for full-time academic faculty recruited to the VA."

With regard to the lessons learned, respondents discussed reassessment of their priorities and recognition of the need to improve their procedures and accountability. They had also learned from site visitors about the importance of RAG and Merit Review and exploration of extra-VA funds. A number also mentioned an increased awareness of the value of maintaining good communications with Veterans groups and congressional representatives. As one respondent said, "Now that the eyes of many are on us, if we do not deliver, with some haste, a high level of productivity, then time may not grant us a second respite."

Ten years later

Of the 49 medical centers whose research was originally assigned to the regional offices in the aftermath of Project Scissors, 23 had no Merit Review or RAG programs in 1978 and so were funded only through the Regional Research and Development Offices. The other 26 programs had one or more approved RAG or Merit Review programs and continued to receive those funds. But the regionalized medical centers received no other direct funding. Instead, they were dependent for their support on the Regional Offices.

By 1988, 15 of the site-visited medical centers originally "zeroed out" had abandoned research. On the other hand, 13 medical centers that had received no research funds at all in fiscal year 1978 (and hence had not been reviewed in Project Scissors) were now receiving research funds. In most cases, the Regional Offices had played a major role in helping those "new" medical centers to establish research programs.

Three programs originally not regionalized became so weak that they were subsequently added to the Regional Offices' responsibility. One of them, after working closely with the Regional Office for four years, revived and regained independence in 1986. Another program that was originally regionalized was made independent in 1982, and a third was expected to become independent late in 1988. There were a few rather spectacular successes. One program that had no research at all in 1978 had three funded Merit Reviews, two RAGs and one Clinical Investigator in 1988. Another had four Merit Review approved investigators in 1988, and a third had three. Another hospital, just beginning its affiliation in 1978 with only one investigator, 10 years later had eight funded

investigators receiving more than $400,000 in annual support.

The overall experience for “regionalized” medical centers over the 10 years from 1978 to 1988 is shown in Figure 17.1 and the top chart in Figure 17.2. It is apparent that many of them remained successful in the face of increasing competition.

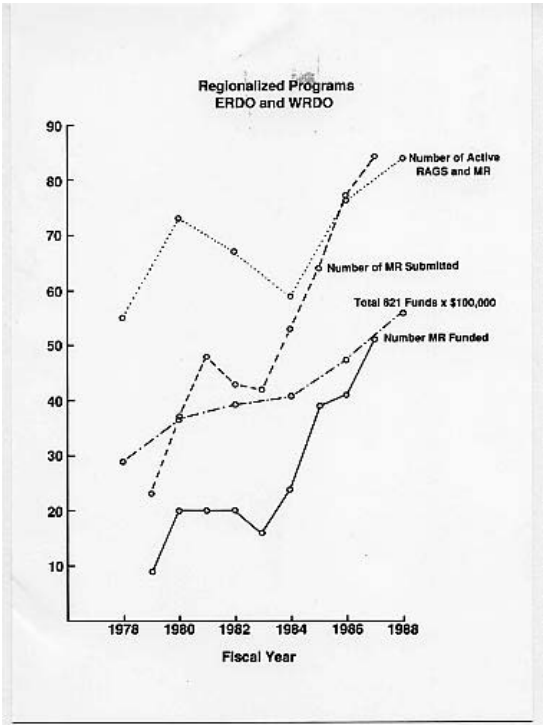


Figure 17.1. Ten years’ experience of the two Regional Research Offices

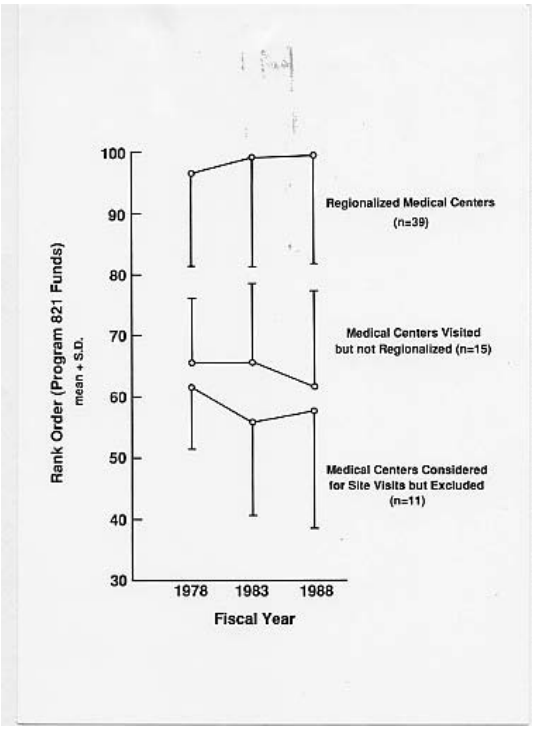


Figure 17.2. Summary of relative funding experience of the three groups of research programs

The independent medical centers

Fifteen medical centers site-visited during Project Scissors were not assigned to Regional Offices. Their research programs seemed to be large enough to constitute a "critical mass" and to be well administered locally. The relative funding positions five and 10 years later for these 15 medical centers is compared in the lower part of Figure 17.2 with those of 11 medical centers in approximately the same funding range that were not site-visited. Surprisingly little difference existed between the two groups of medical centers. If we assume that publication productivity is a reasonable predictor, we would have expected the medical centers that were site-visited to do considerably less well than those that were spared. It is possible that the experience of being site-visited under threatening circumstances stimulated the success of some of the research programs.

Total number of funded medical centers

Perhaps the most unexpected outcome of Project Scissors was stabilization of the total number of medical centers receiving research funds. This number had been declining year by year just before 1978. In fiscal year 1978, 127 medical centers received Medical Research money; in 1988, there were 125. This stabilization most likely can be credited to the Regional Office Chiefs, who actively encouraged and helped investigators from small research programs who wished to compete in research to do so.

Policy impact of Project Scissors

The general principles suggested by the Project Scissors site visitors, and later endorsed by other advisors, remained in place 10 years later and continued in subsequent years. A qualified and motivated person at any VA medical center, with local approval, may compete for research funds through the peer review processes. While the medical centers that have done well usually continue to be those with strong medical school affiliations, no restriction exists on opportunities for investigators from other medical centers.

Chapter 18. The Cooperative Studies Program of the 1970s

As the 1960s progressed, Lawrence Shaw, A.M., increased his role as Chief of the Cooperative Studies Program, establishing a strong Cooperative Studies Evaluation Committee (CSEC) and Cooperative Studies Program Coordinating Centers (CSPCCs). By the end of his tenure in 1972, while he had not yet brought psychiatry studies under the centralized program, the program had become fairly unified. Shaw had come up through the ranks in Central Office. His manner was rather low-key; the success of his leadership depended on eliciting cooperation from those willing to cooperate.[1]

After Shaw retired in the spring of 1972, a search committee sought a new Chief. Meanwhile, William Best, M.D., from Hines (Ill.) acted as Chief. He commuted back and forth to Washington, trying to hold the Cooperative Studies Program together. Best was on the search committee and contacted James Hagans, M.D., Ph.D., to see if he would be interested in taking the job.[2] Hagans had personal reasons to stay in Miami, and turned down the job. However, because the Chief of the Cooperative Studies Program spent considerable time away from his office, it was finally decided that the office need not be based in Washington as long as the Chief made frequent trips to Central Office. So Hagans was approached again, this time with the prospect of establishing an office in Miami from which to administer the Cooperative Studies Program. Dr. Thomas Newcomb, who had recently accepted the position of Director, Research Service, and had not yet come to Washington, was attending a meeting in Hollywood, Fla.. He arranged to meet Hagans, who presented him with an overall plan for how he would run the Cooperative Studies Program. The two reviewed it carefully, and Newcomb agreed that it seemed viable. Hagans accepted the position and immediately began to exert strong leadership in guiding the program in the direction he considered best.[3]

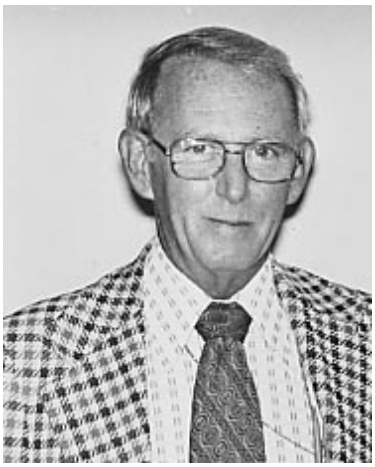


Figure 18.1. James Hagans, M.D., Ph.D.

Organizational changes

Hagans's first effort was to strengthen support of Cooperative Studies by the CSPCCs. In addition to the CSPCCs that had evolved from the old Regional Research Support Centers at Hines and West Haven, Conn. (Chapter 15), he started a CSPCC at Perry Point, Md.. From

the beginning, the Central Neuropsychiatric Research Laboratory (CNPRL) (Chapter 8) at Perry Point had handled statistical and planning support for cooperative studies in psychiatry. The Perry Point CSPCC evolved from that part of CNPRL's activities. Initially, it concentrated on psychiatric cooperative studies, but, as time went on, the responsibilities of the various CSPCCs became evenly distributed.

The CSPCCs at Hines and West Haven, reflecting their experience as Regional Research Support Centers, were still supporting local and regional research in addition to the cooperative studies. At first, Hagans forbade this. The incumbent Chiefs of the Centers were reluctant to change from their old missions, and there were gradual changes in leadership. Later, once the Centers were functioning effectively in support of the nationwide cooperative studies, Hagans relaxed this rule to permit some support of the local research program in exchange for hosting the Centers.

By 1978, the three CSPCCs were working at capacity, and Hagans decided that a new CSPCC was needed on the West Coast. After a competition among medical centers wanting to host such a Center, Palo Alto (Calif.) was chosen as the site for the fourth CSPCC. By 1980, all four CSPCCs were receiving new studies in rotation, covering all types of disciplines. The four Chiefs and their administrators met regularly. Guidelines were established and accepted by all. Administration of the studies was predictable and carefully supervised.

A central pharmacy was established in 1972 at the Washington (D.C.) VA Medical Center. This pharmacy now coordinated all studies using drugs or experimental devices, instead of the ad hoc systems of the past. By the late 1970s, the central pharmacy had outgrown its space at the Washington hospital and was moved to the Albuquerque (N.M.) VA Medical Center. This Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) has grown to become an important player in the program, participating in study design, manufacturing study drugs, keeping close track of study drugs and devices and reviewing the protection of human subjects at the various study sites.[3]

Under Hagans, the Cooperative Studies Program evolved from the rather relaxed program of past times, largely decentralized and encouraging individual initiative, to a much more centralized program with strict attention to statistics and experimental design. Some study groups with a longstanding record of one study after another became less active. As funding became increasingly limited, Hagans worked to find other sources of funds, especially the NIH. He accepted some funds from private firms, but with very careful controls to prevent conflicts of interest.

Dr. Hagans introduced a structured system in which an investigator with an idea for a cooperative study first submitted a "précis," a brief description of the proposed study. A triage group reviewed it and many proposed studies were rejected at this stage. If approved by triage, the proposal was assigned to one of the CSPCCs and a formal planning process began. A committee, including the investigator and other subject-area experts, as well as statisticians from the CSPCC, met several times to complete a plan. The polished proposal eventually went before the Cooperative Studies Evaluation Committee for review. If approved by the CSEC (Appendix IIi), it joined a queue for funding.

Hagans insisted that, in the Cooperative Studies Program, separate groups perform the research, direct the project and evaluate it. Hence, he arranged meetings of the groups of investigators from the cooperating hospitals, the people actually carrying out the research. In addition, an "Operations Committee" reviewed data at regular intervals and directed the project. Of the participants in a cooperative study, only the Chairman also served on this committee, which made such critical decisions as when a participating hospital was not performing adequately and should be dropped, when an arm of the study should be changed or dropped owing to interim statistical results, and when the study had achieved its goal. Evaluation was by the CSEC, which reviewed proposed projects and also ongoing projects to determine if, after three years, they warranted continuation.

In addition, each CSPCC maintained a Human Rights Committee to review each project annually for the protection of subjects. This Committee served as an additional protection, adding a second human rights review to that performed by the Institutional Review Board at each participating medical center.

The studies

The cooperative studies begun in the 1970s (Table 18.1) differed from earlier studies. Each now had a crisply defined goal and clear endpoint. Though some pilot studies were completed, they were limited in scope and limited to defining the feasibility of a specific study. Whereas earlier study groups set their own goals and sometimes freely departed from their primary studies, now an outside group carefully monitored each variation in study design. Some of the longstanding study groups adapted to this new system; others closed. The group of hypertension researchers (Chapter 9) continued to conduct studies under the new system, as did the group of cardiologists and surgeons studying the impact of coronary artery surgery on patients with coronary artery disease. On the other hand, the pulmonary study group that had started with the 1946 tuberculosis trials (Chapter 5) held its last published meeting in 1972 and completed its last report in 1974. The studies of analgesics (Chapter 13) and of psychopharmaceuticals (Chapter 8), which had performed one study after another without CSEC review, closed during the mid-1970s, in part because their leaders found it more difficult to work within the new system.

Sickle cell trait

An important study begun in 1972 determined the clinical importance of sickle cell trait (Hb AS) and glucose-6-phosphate dehydrogenase deficiency (G-6-PD). The Chair was Paul Heller, M.D., of the Chicago West Side VA Medical Center. While the homozygous abnormality (Hb SS), known as sickle cell anemia, causes a well-known illness, it was not known whether the heterozygous Hb AS caused any problems. The impact of G-6-PD, which is fairly common in African Americans, was also unknown. Anecdotal reports had suggested that sickle cell trait would cause an increase in pulmonary infarctions, vascular complications of diabetes, deaths from myocardial infarction and prolonged hospitalization after surgery. G-6-PD was thought to be associated with increased infections, especially pneumonia. Patients with both abnormalities were expected to have longer hospital stays and increased mortality.

Table 18.1. Cooperative studies started during the 1970s

Medical	
Antihypertensive drugs	
Propranolol	1972–1975
Bethedine vs guanethedine in severe hypertension	1972-1975
Efficacy of treatment of mild hypertension (pilot)	1974–1977
Prazosin vs hydralazine	1976–1977
Oxyprenolol vs propranolol	1976–1977
Ticrynafen vs hydrochlorothiazide	1977–1978
Propranolol vs hydrochlorothiazide as first hyptertension rx	1978–1980
Low dose reserpine with chlorthalidone	1978–1980
Captopril	1980–1982
Nadolol	1980–1981
Hepatitis	
Immune vs hyperimmune globulin in needlestick	1972–1976
Immune vs hyperimmune serum globulin in post-transfusion	1973–1976
Hepatitis and drug abuse (observational)	1973–1976
Hepatitis and dentistry	1979–1981
Alcoholic hepatitis	1978–1983
Sickle cell trait	1972–1976
Crohn's Disease	
Prednisone, sulfasalazine, azathioprine, placebo	1972–1977
Sulfasalazine plus prednisone vs prednisone	1976–1977
Medical treatment of heart disease	
Aspirin therapy in unstable angina	1974–1982
Vasodilator therapy of myocardial infarction	1974–1981
Vasodilators in chronic heart failure	1980–1985
Renal failure self-care dialysis	1975–1981
Platelet aggregation in diabetes (aspirin and persantine)	1977–1983
Anticoagulants in the treatment of cancer	1977–1981
Urinary tract infections	1976–1978
Nafcillin therapy in staphylococcal bacteremia	1979–1981
Antiepileptic drugs	1978–1984
Surgical	
Surgery of coronary artery disease	
Stable angina (vein bypass)	1970–1974+20yr FU
Unstable angina (vein bypass)	1976–1982+10yr FU
Radiotherapy vs surgery vs delayed hormonal rx in prostate ca	1974–1981
Bowel preparation for colon operations	
Placebo vs active therapy	1975–1976
Oral vs oral plus iv	1976–1982
Heart valve replacement	1977–1995
Surgical shunt vs medical treatment in alcoholic cirrhosis ascites	1979–1984
Neuropsychiatric	
Drugs and sleep	1975–1977
Treatment of psychotic patients	
Hospital vs community foster care	1970–1974
Day treatment in aftercare	1973–1977
Characteristics of effective ward milieu	1975–1978
Community vs VA nursing home vs hospital	1978–1982
Aphasia	
Individual vs group therapy	1973–1977
Hospital vs home treatment	1979–1983
Alcohol and drug dependence	
LAAM-methadone	1973–1975
Antabuse in rx of alcoholics on methadone maintenance	1977–1980
Antabuse in the treatment of alcoholism	1979–1983
Lithium in alcoholics (pilot)	1979
Dental	
Plaque control	1978–1982
Dental implants	1978–1990
Alloys for dental restorations	1980–1990

This prevalence study screened 65,154 African-American patients at 15 VA medical centers for these two abnormalities. Sickle cell trait was present in 7.8 percent, G-6-DP in 11.2 percent and both abnormalities in 0.9 percent. Clinical data were retrieved from the VA centralized Patient Treatment File on 4,900 patients with sickle cell trait, 1,422 with hemoglobin C trait, 6,741 with G-6-PD and 18,294 with normal hemoglobin. Contrary to expectations, the only significant effects of sickle cell trait were found to be essential hematuria and a small increase in the incidence of pulmonary infarction. G-6-DP and hemoglobin C trait had no adverse effect at all.

This study made it possible to reassurance the many patients found to have sickle cell trait among those screened for sickle cell disease and to alleviate the anxiety of patients with hemoglobin C and G-6-DP. It also provided important information about the frequency of hemoglobin abnormalities, including some of the rarer types. One previously undescribed abnormal hemoglobin (Hemoglobin Arlington Park) was identified among the 65,154 patients screened.[4]

Hepatitis

A series of studies of transfusion-related hepatitis also had an important impact. A study begun in 1969 compared the effectiveness of a preparation of immune serum globulin (ISG) in preventing transfusion-related hepatitis. Incidence of hepatitis was significantly reduced with ISG. Of special importance was the finding that only a quarter of the cases of hepatitis were due to the hepatitis B virus. The others were caused by a previously unrecognized virus, originally called nonA-nonB hepatitis, now known as hepatitis C. When investigators traced the origins of the transfused blood, they found that the nonA-nonB virus was associated with commercially available blood but not with donated blood. This important finding, confirmed in later studies, led to the effort to fill needs for blood from healthy volunteer donors rather than from paid donors who were more likely to carry the nonA-nonB virus.[5]

These findings were confirmed in studies comparing ISG with a serum globulin hyperimmune to hepatitis B (HBIG) in preventing post-transfusion hepatitis B and also needlestick hepatitis.[6] HBIG was more effective than ISG in preventing hepatitis B but not in preventing nonA-nonB hepatitis.

The same investigators searched for evidence of liver disease in asymptomatic parenteral narcotic drug abusers. They found that the majority had laboratory evidence of liver disease, and determined that repeated liver biopsies would be needed to screen adequately for liver disease in these patients.[7]

Another research team studied the efficacy of 30 days of treatment with either a glucocorticosteroid (prednisolone) or an anabolic steroid (oxandrolone) in moderate or severe alcoholic hepatitis. Of the patient population studied, 132 with moderate disease and 131 with severe disease were randomly assigned to one of three treatments: prednisolone, oxandrolone or placebo. In the 30-day period, mortality did not differ significantly in the groups receiving steroid therapy from mortality in the placebo group: 13 percent of moderately ill patients and 29 percent of severely ill patients died. But although neither

steroid improved short-term survival, oxandrolone therapy was associated with improved long-term survival, especially in patients with moderate disease. Among those who survived for one or two months after the start of treatment, the six-month death rate was 3.5 percent after oxandrolone and 19 to 20 percent after placebo (P = 0.02). No consistent long-term effect was associated with prednisolone therapy.[8]

A study of hepatitis and dentistry conducted at 126 VA dental clinics between 1979 and 1981 enrolled 963 dental personnel. At that time, universal precautions (gloves and mask) were not yet widespread in dentistry, and exposure to hepatitis-infected blood and saliva from patients was likely. The study showed that serological evidence of hepatitis B infection increased with the number of years working in the dental environment, from 7.4 percent for those working five or fewer years to 17.8 percent for those working more than 30 years. As a result of this study, immunization to hepatitis B was strongly recommended for dental workers.[9]

Cardiology studies

Surgery for coronary artery disease

Although the group that had been evaluating surgical operations for coronary artery disease (Chapter 13) began to look at patients undergoing coronary artery bypass surgery (CABG) in 1970, they began their definitive study of this procedure in 1972. Between 1972 and 1974, 686 patients were enrolled by 13 VA hospitals.

The criteria for enrolling a patient in this protocol were carefully defined. Randomization to medical or surgical treatment was done centrally by the West Haven (Conn.) CSPCC.

Soon after intake into the study was completed in December 1974, preliminary statistical analysis showed that the 91 patients who had obstruction of the left main coronary artery had a better survival rate if they received surgery than if they were maintained on medical treatment. This result was published and well received.[10]

However, the results associated with the remaining 595 patients, who were followed for an average of 36 months, showed no significant difference between the surgically and medically treated groups.[11] This report stimulated a vigorous response from advocates of the procedure, and considerable controversy.[12]

However, VA supported its cooperative study group, who continued their studies to further refine the circumstances that warranted surgery in this condition. After longer follow-up and further study, they defined other “high risk” conditions, in addition to left main coronary artery obstruction, that favored surgery. The results of these studies, and of subsequent work by others, led to guidelines for the selection of patients who would benefit from CABG.[13]

Aspirin in unstable angina

Twelve VA medical centers participated in a double-blind, placebo-controlled randomized trial of

aspirin treatment (324 mg in buffered solution daily) taken for 12 weeks by 1,266 men with unstable angina (625 taking aspirin and 641 placebo). The incidence of death or acute myocardial infarction was 51 percent lower in the aspirin group than in the placebo group, with no difference in gastrointestinal symptoms or evidence of blood loss between the two groups.

This study showed that aspirin has a protective effect against acute myocardial infarction in men with unstable angina.[14] This was among the first of over 100 studies of the effect of antiplatelet therapy in preventing myocardial infarction and death in patients with unstable angina. The study has been cited countless times in support of using aspirin in these patients, and the therapy that has become standard medical practice.

Acute myocardial infarction with left ventricular failure

Between 1975 and 1981, 11 VA medical centers cooperated in a study of whether the vasodilator nitroprusside would improve outcomes in patients with acute myocardial infarctions complicated by increased left ventricular filling pressure. While nitroprusside was already in widespread use in this situation, it carried the risk of decreased coronary blood flow. An objective study of its risks and benefits was needed. The randomized double-blind, placebo-controlled trial assessed the efficacy of a 48-hour infusion of sodium nitroprusside in 812 male participants with presumed acute myocardial infarction and left ventricular filling pressure of at least 12 mm Hg. The results were complex. Treatment did not significantly affect overall mortality rates at 21 days (10.4 percent in the placebo group and 11.5 percent in the nitroprusside group) and at 13 weeks (19.0 percent and 17.0 percent, respectively). However, timing was critical: The drug had a deleterious effect in patients whose infusions were started within nine hours of the onset of pain (mortality at 13 weeks, 24.2 percent vs. 12.7 percent; $P = 0.025$), but it had a beneficial effect in those whose infusions were begun later (mortality at 13 weeks, 14.4 percent vs. 22.3 percent; $P = 0.04$). The investigators concluded that nitroprusside should probably not be used routinely in patients with high left ventricular filling pressures after acute myocardial infarction, but that patients with persistent pump failure might receive sustained benefit from short-term nitroprusside therapy.[15]

Chronic congestive heart failure

Congestive heart failure continues to be a major cause of death among Veterans as well as in the general population. In 1980, 11 VA medical centers undertook a study to see whether treatment with vasodilators would improve the life span of patients with this disorder. They randomly assigned 642 consenting men with impaired cardiac function and reduced exercise tolerance who were already taking digoxin and a diuretic for their heart failure to receive additional double-blind treatment. This involved placebo, prazosin (20 mg per day) or the vasodilating combination of hydralazine (300 mg per day) and isosorbide dinitrate (160 mg per day). Follow-up averaged 2.3 years (range, six months to 5.7 years). At two years, mortality was reduced by 34 percent among patients treated with hydralazine and isosorbide dinitrate ($P<0.028$), 25.6 percent in the hydralazine-isosorbide dinitrate group versus 34.3 percent in the placebo group; at three years, mortality was reduced 36 percent (36.2 percent versus 46.9 percent). Mortality in the prazosin group was similar to that in the placebo group. Left ventricular ejection fraction, a measure of left ventricular function,

rose significantly at eight weeks and at one year in the group treated with hydralazine and isosorbide dinitrate but not in the placebo or prazosin groups.

This study showed that the addition of hydralazine and isosorbide dinitrate to the therapeutic regimen of digoxin and diuretics in patients with chronic congestive heart failure can have a favorable effect on left ventricular function and mortality.[16]

Valvular heart disease

Improvements in cardiac surgery have allowed patients with damaged heart valves to receive valve replacements that correct their disorder. Both mechanical valves and animal (porcine) valves have been used, and both have their advantages and disadvantages. Mechanical heart valves are durable but are thrombogenic (tend to cause clotting), requiring that patients take anticoagulants. In contrast, bioprosthetic valves are less thrombogenic but are of limited durability due to tissue deterioration. To compare the advantages and disadvantages of these two approaches, between 1977 and 1982 13 participating VA medical centers randomized 575 patients who needed replacement of their mitral or aortic heart valve to receive either a mechanical or porcine valve.

During an average follow-up of 11 years, no difference was found between the two groups in the probability of death from any cause or of any valve-related complication. A much higher rate of structural valve failure was experienced by patients who received bioprosthetic valves (11-year probability, 0.15 for aortic valves and 0.36 for mitral valves) than was experienced by those who received mechanical valves (no valve failures; $P<0.001$). However, this difference was offset by a higher rate of bleeding complications in patients with mechanical valves than in those with bioprosthetic valves (11-year probability, 0.42 and 0.26, respectively; $P<0.001$) and by a greater frequency of periprosthetic valvular regurgitation in patients with mechanical mitral valves than in those with mitral bioprostheses (11-year probability, 0.17 and 0.09, respectively; $P = 0.05$).

From the results of this study and the review of similar studies by others, the authors were able to provide guidance about which type of valve is better for a particular patient.[17]

Antibiotic prophylaxis in colon surgery

During the 1970s, some surgeons were using oral antibiotics to supplement mechanical bowel cleansing in preparing patients for surgery of the colon and rectum. This use, however, was controversial. In general, using antibiotics to prevent infection rather than treat it was considered unwise: Bacterial flora were likely to become resistant to the antibiotics used, promoting the spread of resistant organisms in the individual patient and in the environment. On the other hand, small studies of the use of prophylactic oral antibiotics suggested that these fears were unfounded and that many infections could be avoided by prophylactic use of antibiotics.

To gain a better understanding of the potential value of antibiotic prophylaxis, a cooperative study was designed in which oral antibiotics (neomycin and erythromycin) or placebo were given the day before surgery in addition to vigorous mechanical cleansing of the bowel. The original plan had been to study 287 patients, the number projected for a clear-cut answer if infection rates were 20 percent without oral antibiotics and 10 percent with them. The difference revealed by the study was

even more dramatic. Forty-three percent of patients in the placebo group developed infections, compared to only 9 percent of those receiving antibiotics the day before surgery.

This study reflected the wisdom of the system Hagans had established. Only the monitoring Operations Committee saw the data and its statistical analysis on a periodic basis. The members of the Operations Committee did not actually enroll or follow the patients in the study, so there was no way that their knowledge of the preliminary results could affect the objectivity of the study. When the Operations Committee reviewed the data from the first 116 patients, the answer to the study question was clear: Antibiotic treatment conferred a benefit. At that point, the Operations Committee announced the results and stopped the study. Henceforth, patients were no longer jeopardized by receiving the less favorable treatment.[18] All would receive the benefit of prophylactic antibiotics to reduce the likelihood of infection.

On the other hand, a later study, which examined the benefit of adding intravenous antibiotics to the established preparatory regimen of mechanical bowel cleaning together with oral antibiotics, failed to show a significant advantage. In order to establish this negative finding, it was necessary to study 1,128 patients over a five-year period. Even then, the results with added IV antibiotic were somewhat better, though not significantly so. A doubt remained that an even larger study might uncover a small preference for adding the IV antibiotic. Unlike the first study, which changed the practice of surgeons both in VA and elsewhere, this later study had much less impact[19] despite the tremendous effort it involved.

Recurrent urinary infections in men

The natural history and treatment of recurrent urinary infections in women had been well studied by the 1970s, but appropriate treatment in men was still not established. Studies in women had shown that antibiotic treatment of bladder infections was effective after only 10 days of treatment, while infections of the upper urinary tract required prolonged therapy. At three VA medical centers, 38 male patients with recurrent urinary infections, most with prostatic infection, were treated in a double-blind study with either 10 days or 12 weeks of antibiotic therapy. Most patients given only 10 days' treatment had recurrences with the same organism within four weeks.[20] The cure rate was better with 12 weeks, but the difference failed to reach significance ($p=.06$).

Anticoagulants in the treatment of cancer

By the end of the 1970s, considerable evidence had accumulated implicating blood coagulation reactions in the growth and spread of malignancy. It was found that platelets may accumulate on embolic tumor cells and facilitate their adhesion to the endothelium at distant sites, perhaps by enhancing blood coagulation reactions. Another possibility was that platelets may promote tumor cell proliferation by contributing a growth-promoting factor or through interactions mediated by prostaglandins. Inhibition of tumor growth and spread by platelet-inhibitory drugs had been demonstrated in several experimental tumor systems, and preliminary data suggested that similar effects were seen in human malignancy.[21]

To evaluate the importance of this evidence that spread of malignancy is associated with blood clotting mechanisms, between 1976 and 1981, 13 VA medical centers studied the effect

of warfarin anticoagulation on outcome in patients with cancer of the lung, colon and rectum, prostate, and head and neck. The most dramatic finding was that warfarin doubled the survival time of patients with small-cell carcinoma of the lung. Median survival for 25 control patients was 24 weeks; for 25 warfarin-treated patients, it was 50 weeks. This difference could not be accounted for by differences between groups in performance status, extent of disease, age or sex. The survival advantage associated with warfarin administration was observed both for patients with extensive disease and for those who failed to achieve complete or partial remission. The warfarin-treated group also demonstrated a significantly increased time to first evidence of disease progression. These results suggested that warfarin was useful in the treatment of small-cell carcinoma of the lung and also supported the hypothesis that the blood coagulation mechanism is involved in the growth and spread of cancer in humans. This result was so definitive that the Operations Committee decided to stop adding patients in the study arm involving small-cell lung cancer.[22]

No differences in survival were observed between warfarin-treated and control groups for the other cancers studied.[23]

Care of patients with schizophrenia

Psychotropic drugs (Chapter 8) revolutionized the care of schizophrenic patients, but they did not cure them. A series of cooperative studies carried out in the 1970s, led by Margaret Linn, Ph.D., a social worker at the Miami VA Medical Center, studied the post-hospital treatment of these patients. One of the most important of these studies compared the effect of differing characteristics of day treatment programs. In this study, conducted in ten VA Day Treatment Centers between 1973 and 1977, schizophrenic patients who were eligible for day treatment at the time of hospital discharge were randomly assigned to receive day treatment plus drugs or drugs alone. They were tested before assignment and at six, 12, 18 and 24 months on social functioning, symptoms and attitudes. Community tenure and costs were also measured. The Day Treatment Centers were described on process variables every six months for the four years of the study.

Some Centers were found to be more effective than drugs alone in treating chronic schizophrenia patients, and others were not, although all of the Day Treatment Centers improved the patients' social functioning. Six of the Centers were found to significantly delay relapse, reduce symptoms, and change some attitudes. Costs for patients in the successful Centers were not significantly different from costs for the group receiving only drugs. The Centers with the most successful outcomes offered more occupational therapy and a sustained reassuring environment. Centers with a treatment philosophy encouraging high patient turnover had poorer results. Surprisingly, poorer results were also associated with Centers that had more professional staff hours and group therapy.[24]

References

1. Interview with Lawrence W. Shaw, M.S., February 3, 1994 at Mr. Shaw's home in Gainesville, Florida.

2. Interview with William Best, M.D., April 26, 1994 at a hotel lobby in Washington, DC.

3. Telephone interview with James Hagans, M.D., Ph.D., April 24, 1988.

4. Heller, P., Best, W.R., Nelson, R.B. and Becktel, J., "Clinical implications of sickle-cell trait and glucose-6-phosphate dehydrogenase deficiency in hospitalized black male patients." *N Eng J Med*, 1979. **300**: 1001-1005.

5. Seeff, L.B., Wright, E.C., Zimmerman, H.J. and McCollum, R.W., "VA cooperative study of post-transfusion hepatitis, 1969-1974: incidence and characteristics of hepatitis and responsible risk factors." *Am J Med Sci*, 1975. **270**: 355-362.

6. Seeff, L.B., Wright, E.C., Finkelstein, J.D., Greenlee, H.B., Hamilton, J., Leevy, C.M., Tamburro, C.H., Vlahcevic, Z., Zimmon, D.S., Zimmerman, H.J., Felsher, B.F., Garcia-Pont, P., Dietz, A.A., Koff, R.S., Kiernan, T., Schiff, E.R., Zemel, R. and Nath, N., "Efficacy of hepatitis B immune serum globulin after accidental exposure." *Lancet*, 1975: 939-941.

7. Seeff, L.B., Zimmerman, H.J., Wright, E.C., Schiff, E.R., Kiernan, T., Leevy, C.M., Tamburro, C.H. and Ishak, K.G., "Hepatic disease in asymptomatic parenteral narcotic drug abusers: a Veterans Administration collaborative study." *Am J Med Sci*, 1975. **270**: 41-47.

8. Mendenhall, C.L., Anderson, S., Garcia-Pont, P., Goldberg, S., Kiernan, T., Seeff, L.B., Sorrell, M., Tamburro, C.H., Weesner, R., Zetterman, R., Chedid, A., Chen, T., Rabin, L. and Veterans Administration Cooperative Study on Alcoholic Hepatitis, "Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone." *N Engl J Med*, 1984. **311**: 1464-1470.

9. Schiff, E.R., de Medina, M.D., Kline, S.N., Johnson, G.R., Chan, Y.-K., Shorey, J., Calhoun, N. and Irish, E.F., "Veterans Administration cooperative study on hepatitis and dentistry." *JADA*, 1986. **113**: 390-396.

10. Takaro, T., Hultgren, H.N., Lipton, M.J., Detre, K.M. and participants in the study group, "The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease II: Subgroup with significant left main lesions." *Circ*, 1976. **54**: III-107-117.

11. Murphy, M.L., Hultgren, H.N., Detre, K.M., Thomsen, J., Takaro, T. and Participants, "Treatment of chronic stable angina: A preliminary report of survival data of the randomized VA cooperative study." *New Engl J Med*, 1977. **297**: 621-627.

12. Jones, D.S., "Visions of a cure; visualizations, clinical trials and controversies in cardiac therapeutics, 1968-1998." *Isis*, 2000. **91**: 504-541.

13. Kirklin, J.W., Akins, C.W. and Blackstone, E.H., "ACC/AHA guidelines and indications for coronary artery bypass surgery. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Coronary Artery Bypass Surgery)." *Circ*, 1991. **83**: 1125-1173.

14. Lewis, H.D., Davis, J.W., Archibald, D.G., Steinke, W.E., Smitherman, T.C., Doherty, J.E., Schnaper, H.W., LeWinter, M.M., Linares, E., Pouget, J.M., Sabarwal, S.C., Chesler, E. and DeMots, H., "Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina." *N Engl J Med*, 1983. **309**: 396-403.

15. Cohn, J.N., Franciosa, J.A., Francis, G.S., Archibald, D.G., Tristani, F., Fletcher, R., Montero, A., Cintron, G., Clarke, J., Hager, D., Saunders, R., Cobb, F., Smith, R., Loeb, H. and Settle, H., "Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure. Results of a Veterans Administration Cooperative Study." *N Engl J Med*, 1982. **306**: 1129-1135.

16. Cohn, J.N., Archibald, D.G., Ziesche, S., Franciosa, J.A., Harston, W.E., Tristani, F., Dunkman, W.B., Jacobs, W., Francis, G.S., Flohr, K.H., Goldman, S., Cobb, F.R., Shah, P.M., Saunders, R., Fletcher, R., Loeb, H., Hughes, V.C. and Baker, B., "Effect of vasodilator therapy on mortality in chronic congestive heart failure." *N Engl J Med*, 1986. **314**: 1547-1552.

17. Hammermeister, K.E., Sethi, G.K., Henderson, W.G., Oprian, C., Kim, T., Rahimtoola, S. and Veterans Administration Cooperative Study on Valvular Heart Disease, "A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis." *N Engl J Med*, 1993. **328**: 1289-1296.

18. Clarke, J.S., Condon, R.E., Bartlett, J.G., Sherwood, L., Gorbach, L., Nichols, R.L. and Ochi, S., "Preoperative oral antibiotics reduce septic complications of colon operations." *Ann Surg*, 1977. **186**: 251-259.

19. Condon, R.E., Bartlett, J.G., Greenlee, H.B., Schulte, W.J., Ochi, S., Abbe, R., Caruana, J.A., Gordon, E., Horsley, S., Irvin, G., Johnson, W., Jordan, P., Keltzer, W.F., Lempke, R., Read, R.C., Schumer, W., Schwartz, M., Storm, R.K. and Vetto, R.M., "Efficacy of oral and systemic antibiotic prophylaxis in colorectal operations." *Ann Surg*, 1983. **118**: 496-502.

20. Smith, J.W., Jones, S.R., Reed, W.P., Tice, A.D., Deupree, R.H. and Kaijser, B., "Recurrent urinary tract infections in men. Characteristics and response to therapy." *Ann Int Med*, 1979. **91**: 544-548.

21. Zacharski, L.R., Henderson, W.G., Rickles, F.R., Forman, W.B., Cornell, C.J., Jr., Forcier, R.J., Harrower, H.W. and Johnson, R.O., "Rationale and experimental design for the VA

Cooperative Study of Anticoagulation (Warfarin) in the Treatment of Cancer." *Cancer*, 1979. **44**: 732-741.

22. Zacharski, L.R., Henderson, W.G., Rickles, F.R., Forman, W.B., Cornell, C.J., Jr., Forcier, R.J., Edwards, R., Headley, E., Kim, S.H., O'Donnell, J.R., O'Dell, R., Tornyos, K. and Kwaan, H.C., "Effect of warfarin on survival in small cell carcinoma of the lung. Veterans Administration Study No. 75." *Jama*, 1981. **245**: 831-835.

23. Zacharski, L.R., Henderson, W.G., Rickles, F.R., Forman, W.B., Cornell, C.J., Forcier, J., Edwards, R.L., Headley, E., Kim, S.-H., O'Donnell, J.F., O'Dell, R., Tornyos, K. and Kwaan, H.C., "Effect of warfarin anticoagulation on survival in carcinoma of the lung, colon, head and neck, and prostate." *Cancer*, 1984. **53**: 2046-2052.

24. Linn, M.W., Caffey, E.M., Klett, C.J., Hogarty, G.E. and Lamb, H.R., "Day treatment and psychotropic drugs in the aftercare of schizophrenic patients." *Arch Gen Psychiatry*, 1979. **36**: 1055-1066.

(Intentionally Blank)

Chapter 19. Beginnings of Health Services Research and Development in VA

Today's VA Health Services Research and Development (HSR&D) Service is a major player in the overall research effort in VA and a leader in its field. It took shape toward its present form during the 1970s, with its major growth occurring after 1990, but the recent program has its roots in multiple earlier efforts.

Maximizing both the quality and cost-effectiveness of medical care has always been a central concern for VA. As early as 1929, the Veterans' Bureau's Medical Council (Chapter 1) asked the Bureau's Research Section to compare the standards of medical care in Bureau hospitals with civilian hospitals. After reviewing the data presented to them by the Research Section, the Council concluded: "There exist at present no satisfactory standards according to which treatment can be appraised. Neither civilian nor bureau institutions rate treatment according to the same, let alone uniform, standards."[1]

Today, the Bureau's descendant, the Department of Veterans Affairs, maintains a vigorous and well-coordinated HSR&D program. It employs an interdisciplinary approach that draws on all relevant scientific methodologies and applies the scientific method to evidence-based management to assure that health care decisions will be based on fact. Improving the practice of medicine within the context of reality is its central goal.

This approach is the result of the combination and evolution of many methodologies. These include the operations research methods developed during World War II, psychometrics (the mathematical, especially statistical, design of psychological tests and measures), economics, decision analysis and management theory as well as aspects of computer science and other disciplines. This chapter traces some of these methodologies and their early intertwining into the emerging HSR&D program of the 1970s.

The Fort Howard Program and the Management Systems and Standards Service

Signs of VA's first formal effort to conduct research in how to improve health services appear in 1958, when a research program was launched by Linus Zink, M.D., head of the Administrative Section in the Central Office Department of Medicine and Surgery. To organize and direct this program, he recruited John Willoughby, then Assistant Manager at the Ann Arbor (Mich.) VA Hospital. The charge of this new Management Systems and Standards Service was to conduct research in developing efficient hospital systems, an effort fully backed by the Director of Professional Services at that time, Irvin Cohen, M.D.

Willoughby directed the new Service from the Washington office, where Peter Korstad performed generalized hospital studies. For more innovative studies, Willoughby set up a unit at the Fort Howard (Md.) VA Hospital. This unit's original responsibility was to work with

hospital staff to minimize waste. Although there were concerns among the local staff that the findings could lead to layoffs, Cohen made it clear that the Fort Howard group's mission was not to achieve local savings, but to develop data that might be used in developing national priorities. Initially, the Fort Howard group did not address professional areas such as physician staffing, even though Cohen expressed the intention of extending the studies in that direction.[2]

Leon Gintzig, who held a Ph.D. in Hospital Administration, started and led the Fort Howard operation. Around February 1960, John Peters was assigned to Fort Howard as Associate Director of what was now called the Health Services R&D Service. The plan was to locate HSR&D on a research floor at the new Washington, D.C., VA hospital, which was under construction. Until it was completed, the group worked at Fort Howard.

At the Fort Howard Hospital, the HSR&D unit established VA's first intensive care unit to test the value of individual monitoring. They also tested a concept for reorganizing smaller hospitals by centralizing the administrative management into a single service. This was tried out at a half dozen test facilities.

Aware of the need to have medical information stored in a manner enabling easy extraction and analysis of data, they also tried to get a medical information system keyed into a computer but lacked the requisite technical competence to do this effectively. After the program was moved to the new Washington VA Hospital, this effort evolved into the Automated Hospital Information System (AHIS).[3]

The Central Office Administrative Research Program

In 1963, a Committee on Administrative and Developmental Research was formally announced to the field, with Peter Korstad as Chairman and seven other members including Charles Chapple M.D. of Research Service; Clyde Lindley, M.A., from psychopharmacology studies; and Daniel Rosen, the highly respected head of the statistics program. The Committee was to "review projects submitted for administrative and developmental research to recommend priorities for their initiation throughout the VA system." This included plans for the administrative and developmental research laboratory at the VA Hospital in Washington, D.C.[4] Three years later, in 1966, this Committee was replaced by an Administrative Research Committee, which was charged with general advice and proposal review[5] and whose members were mostly ACMDs. At that time, Korstad was made an alternate to the chairman, and R.E. Smith, of the Administrative Research Staff, became Executive Secretary.

By 1966, the Administrative Research Program had been placed within the Systems and Standards Service with John M. Buchanan as Director and William H. Kirby, M.D. as Deputy Director.[6] Its mission included conducting formal studies to test hypotheses related to administrative aspects of a health services operation. The program also was expected to conduct basic research, defined as "investigative activity directed toward an increase in

knowledge (in fields relevant to VA's goals) rather than a practical application thereof". In addition, the Administrative Research Program's mission included involvement in developmental research in the form of "investigative activity in which the systematic use of knowledge is directed toward the production of more useful services, devices, systems and methods."[7]

During the following year, the Administrative Research Program solicited cooperation in a survey of job attitudes being undertaken by a group of Ph.D. scientists at the VA hospital in Downey, Ill. A project reviewing utilization and efficacy of Incentive Therapy programs was announced in 1965.[8]

In 1968, the Administrative Research Committee was abolished, with the explanation that: "With the reorientation of the Administrative Research program to emphasize central planning and direction, the Committee is no longer essential."[9] The next year, a circular soliciting suggestions for Health Services Research and Development projects was distributed to field hospitals.[10]

The Automated Hospital Information System (AHIS)

Meanwhile, the efforts at computerization begun at Fort Howard were expanding at the new Washington VA Hospital, which boasted a new computer system far more powerful than the one the Fort Howard unit had tried to use. The envisioned goal was to find a means to contend with a major problem: "the reams of paperwork connected with providing medical care and treatment for Veterans (that) have always been the bane of doctors, nurses and other professionals in the Veterans Administration."[11]

During the 1957-1961 period under VA Administrator Sumner Whittier, a major effort was made to automate the paperwork activities of the VA's Insurance and Veterans Benefits departments.[11] The staggering load of paperwork in the patient care program was a compelling reason to try to extend this technology to the VA hospital system. In 1961, Chief Medical Director Middleton set in motion projects to use computer technology to increase efficiency and quality in VA hospitals, with the goal of total automation of the hospitals' information systems. Among its many positive effects would be that all necessary information concerning a patient, from admission to discharge, would be recorded electronically. Armed with this information, the admitting physician would then give the Veteran an examination to determine the needs for hospitalization. If the examination confirmed the need, the system would automatically check availability of a suitable bed, and indicate the location (such as ward and building) of that bed to the admitting physician. Other relevant services within the hospital would simultaneously be notified about support services that were needed. Subsequently, instructions concerning patient needs (e.g., prescriptions to the pharmacy and dietetic needs) would continue to flow through the system.

Regional data processing centers were planned to assemble all this information and service

the information needs of designated VA medical installations within specific geographical areas.[11]

Work toward this utopian goal began in 1961, when, under a VA contract, the Systems Development Corporation (SDC) in Los Angeles began work on computerizing clinical care. It analyzed data from the West Los Angeles VA Hospital and set up simulations of ward activities, bed control, laboratories and other hospital functions.

That same year, work toward this automation goal also began in VA Central Office. Lawrence Christianson, M.D., who had been Chief of Medicine and Chief of Staff at the Fort Meade (S.D.) VA Hospital, came to Central Office in early 1961 as Assistant Director of Medical Service. Later that year, he was put in charge of the 50-member data processing staff charged with developing automated systems for payroll, personnel, management control, clinical applications and research.

By 1965, the two projects were combined to form the Automated Hospital Information System (AHIS), now using an up-to-date computer facility located at the new Washington VA Hospital. The goal was to create a prototype for a nationwide management information system, working closely with nurses and doctors at the hospital to design, develop and program simulations of all hospital activities.

The first AHIS applications, for admissions and discharges, presented little difficulty. But the study of pharmacy operations required complex interaction with the medical staff, nurses, pharmacists and administrative staff working in the pharmacy. While the hospital was enthusiastic about this effort, Central Office officials were nervous about it, so programmers' efforts were redirected to automating radiology. In retrospect, this system, requiring expensive mainframe hardware, was ahead of its time. According to Dr. Christianson, "Someone did a cost-benefit analysis of this system about 1969 and found that the whole system might save 2 FTEE (employees)."[12]

During his period as ACMD/R&E (1968-1969), Thomas Chalmers, M.D., had some acquaintance with AHIS during the day he spent each week at the Washington VA Hospital. At that time, Chalmers championed the effort to computerize all patient information, but in retrospect he felt that the initiative was premature as the available hardware and software weren't up to the job.[13]

In 1969, Christianson moved to Research Service as Program Chief in Neurology and Regional Coordinator for the Northeast Region. Oren Skouge, M.D., who had left his position as Deputy Chief Medical Director after a change in administrative leadership, spent most of 1970 at the Washington hospital working on AHIS. By this time, the administrative records

had been automated and the AHIS staff were working on automating the professional records. Skouge also expressed the opinion that the technology for this task simply hadn't been there. Another problem was that doctors refused to use a keyboard to enter patient information. To make matters worse, maintaining the large IBM computer consumed several hundred thousand dollars annually.[14]

By 1972, when Al Gavazzi became Director of the Washington VA Hospital, the Administrative Research Program there had been split into three groups. The first group was working on the automation of direct patient care problems, led by Hubert Pipberger, M.D., who had begun computerizing EKGs while the hospital was still located in the Mt. Alto section of Washington. Other hospital clinicians also saw computers as the answer to patient care problems and were trying to perfect various types of patient care systems.

The second group, the AHIS central group, included people with administrative interests who were trying to place medical administration and medical records on the computer and make the computerized system clinically useful.

The third group, the former Health Systems Research unit that had moved from Ft. Howard to Washington when the new hospital opened, now comprised a staff of seven people headed by Leon Gintzig. They were addressing practical problems of hospital layout.

Wendell Musser, M.D., who became ACMD for Planning and Evaluation in 1970, was responsible for Central Office coordination of AHIS as well as for other aspects of Health Services R&D. In his opinion, AHIS was "a huge bottomless pit." By 1970, it had already cost $2.4 million, with little to show in the way of visible product or value added to administrative efficiency or care. A formal review of AHIS brought unfavorable results, and in1972, the decision was made to reduce further support for AHIS development.

After that, there was little widespread support for AHIS, and funding became difficult. The core funding came from the Department of Data Management in Central Office and the Washington hospital's medical staff, who had remained enthusiastic about the project.

The first effort under Gavazzi involved placing computers in nursing stations to allow computerization of orders to the pharmacy and lab and then radiology. Centralization of the patient record was also attempted. Staff physicians, especially neurosurgeon Paul Schaeffer, M.D., devoted considerable time to this endeavor.

Central Office officials who felt that the AHIS project was ill-advised called this system of local support the "Underground Railway." But according to Gavazzi, this Central Office opposition was not universal. Key officials such as James Pittman and John Chase, and later Donald Custis and W.J. Jacoby, were supportive.[15]

Walter Whitcomb, M.D., recalled that when he arrived in VACO in 1979 to head the medical computer program, his whole team spent some time at the Washington VA Medical Center learning about AHIS. Terminals were in use on all clinical units. By this time, the ICU had been automated. Whitcomb recalled that two or three programmers working in the MUMPS language at the medical center were working on AHIS. It was a very expensive program, and as computer technology advanced, it was increasingly viewed as archaic. [16]

Nevertheless, AHIS continued to function at Washington VA Hospital through the 1970s and into the early 1980s, and the staff at the facility supported it. According to Jack Divers, who joined the AHIS team in 1975 as a programmer in IBM assembly language, the program ran on an IBM 360-40 mainframe computer, with all code in IBM assembly language. Well before Divers's arrival, the program had been completed and was then, in 1975, in its maintenance phase. The 52 terminals scattered throughout the hospital handled a variety of tasks, including administrative matters (patient admissions, discharges and transfers); clinical laboratory tests, which could be ordered on the computer from the wards and results sent to the ward computer terminals; and radiology scheduling.

No health care provider was specifically assigned to AHIS, so each clinical service designated its own coordinator and the AHIS staff would meet with doctors to talk about their needs. Many physicians recognized the potential of the AHIS for improving health care in myriad ways; the Chief of Radiology would meet with technicians to discuss improvements that could be made to the radiology subsystem, and other groups of subject-matter specialists would also get together to discuss their needs.

The computer system proved cumbersome. Six times a day, it was necessary to close it down for 10 minutes to back it up onto tape. And it was very demanding: A staff of 20 were on hand simply to maintain the program. The development phase had ended, but at its peak at least 50 people worked on the system. Still, in Divers's opinion, the actual design of the system was very good.

An audit staff of VA people not associated with AHIS reviewed all proposed changes to the system. If a hospital service requested a change, an auditor reviewed it and then passed it on to a programmer. The resulting change was again reviewed by the auditor, who then might give permission to implement it on the system. Testing any part of the system, however, was very expensive. No duplicate system existed, so all changes had to be implemented on a test set of disks. At 2 a.m., the system was shut down until 5 a.m., to allow time to install the test system.

In 1975, the AHIS staff had a long-term plan to replace the hardware, which was by then grievously outdated. Procurement problems, however, prevented them from getting new equipment and the AHIS systems was forced to continue to run on the old equipment.

The system-wide computerized hospital information system eventually developed by VA differs from AHIS, but much of the basic design for data flow used in AHIS remains embedded in the current system.[17]

Health Services Research and Development Service in VA Central Office

Despite the efforts mentioned above, the Central Office leadership identified a need for more progress in the study of health care delivery. In 1971, Dr. Lionel Bernstein, former Director of Research Service, was given a special assignment to review hospital operations. His review resulted in a paper identifying a need for a more active program in Health Services Research. Leon Bernstein, Ph.D., who also had just left Research Service, was assigned to be Director of a newly constituted HSR&D Service that incorporated the Administrative Research Service as well as other functions.[18]

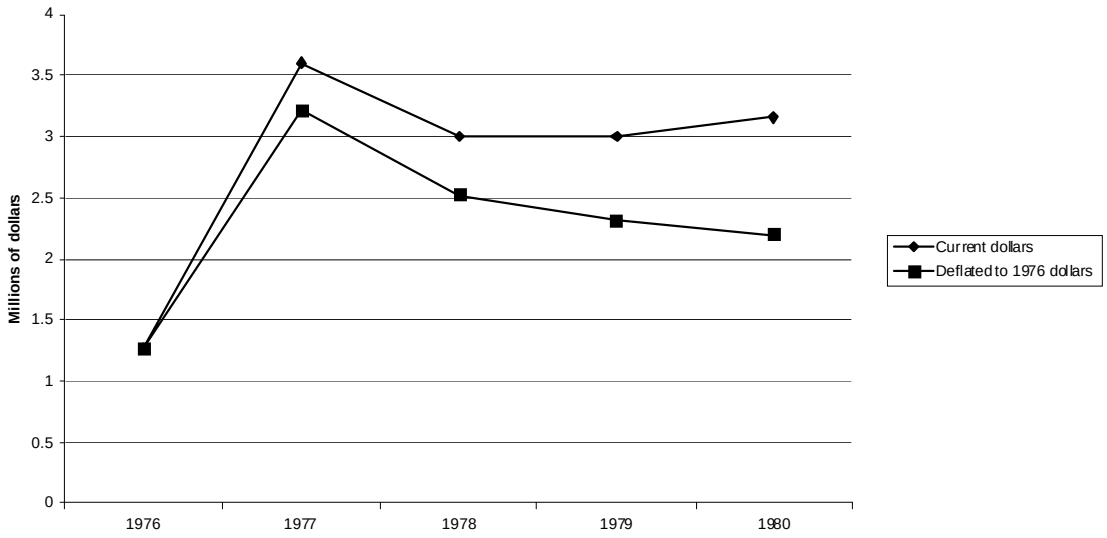
In October 1972, Carleton Evans, M.D., succeeded Leon Bernstein as Director of the HSR&D Service, which continued to be located in the Office of Planning and Evaluation, under Wendell Musser, M.D. Evans had been at the San Francisco VA Hospital, where he had built up an outpatient department. While there, a medical school classmate, Dr. Gerald Charles, returned from the military as a resident. Charles and Evans collaborated on a Health Services Research and Development study of physician extenders. They trained young people from the inner cities to perform triage using protocols and to function as physician's assistants. Charles had learned about this approach in the Army, where trained corpsmen successfully performed triage. The study was funded by the Federal Model Cities Program. When Wendell Musser heard about this activity, he visited San Francisco and recruited Evans. At that time, recalled Evans, HSR&D Service focused primarily on "industrial engineering." Without any money of its own, the Service was forced to seek CMD approval to do something beyond the routine. Consequently, very little research was going on and, in Evans's opinion, the studies being done when he arrived in Central Office were mundane.

Figure 19.1. Carleton Evans, M.D.

The newly conceptualized Health Services Research and Development Service began work in earnest with Evans as Director. Thomas Newcomb, M.D., who had been Director of Research Service and was now ACMD/R&D, was Evans's new boss. At first, the HSR&D Service, which had a staff of some 125 people, was given responsibility for VA's computer design and installation throughout the agency in addition to establishing health services research as a vigorous activity. Most of its computer staff, however, lacked the requisite training and appropriate experience for the task, and it seemed unlikely that they were up to the job. By 1976, the computer responsibility had moved to a separate office, making it possible to concentrate on starting a true research program in Health Services Research.

Until then, HSR&D lacked its own budget and, except for a handful supported from Medical Research funds, projects were supported by the patient care budget. Newcomb and Evans worked strenuously to achieve a line item in the congressional budget to support HSR&D. In 1976, some funds were found to support new programs, and in October 1976 (for the fiscal year 1977 budget), HSR&D was written into VA's legislation with the addition of the words "including… health services research." The 1977 HSR&D budget was $3.6 million, and it remained at about $3 million until a gradual rise beginning in 1983.

Figure 19.2 Health Services Res. and Dev. budget, 1976-1980



The HSR&D Service continued to respond to short-term needs of the medical department with "management-type" studies conducted by Central Office staff or by contractors, until a field-based research program was introduced in the mid-1970s. In 1975, VA hospitals were invited to apply for support of projects ("investigator-initiated research."). A committee of

experts assembled to provide peer review, and the first review meeting was held in June 1975. The results were disappointing: The proposed investigators were inexperienced in health services research and lacked guidance on how to prepare a health services research protocol. The committee provided extensive advice to the authors of those proposals that seemed to have merit. Some of these were rewritten and resubmitted for the next meeting of the committee, which continued to hold semiannual review meetings. By October 1976, when funds to support projects were in hand, seve projects of the 55 that were reviewed were ready to be funded. Over the next four years, submission rates remained modest, and funding was similarly selective (Table 19.1), with the review board holding to a high standard

Table 19.1. Beginnings of Investigator-Initiated Health Services Research and Development

	Fiscal Year				
	1976	1977	1978	1979	1980
Investigator-initiated projects*					
Number reviewed	55	64	74	60	44
Number funded	7	9	15	14	8
Percent funded	13	14	20	23	18

*Information provided by Carol Girard of the Management Decision and Research Center, VA Boston Healthcare System, October 11, 2001.

In addition to this nascent intramural program, the young Health Services Research program supplemented its intramural efforts with contracts, just as the early Medical Research program had depended heavily on contracts to investigators outside of VA. Contracts were negotiated when there were "emergent high-priority research needs."[19]

The main challenge of Health Services Research in the 1970s was to build capacity, the same challenge that had faced the Medical Research program in the 1940s and 1950s. Without increased capacity, expansion of intramural research was impossible. Evans tried several approaches to meet this challenge. In the Investigator-Initiated Research program, the early review committee provided instruction as well as evaluation for aspiring researchers. In addition, a program of university affiliations was established, with an associated training program.

In 1975, the National Center for Health Services Research of the Department of Health, Education and Welfare issued a grant solicitation for health services research centers to "conduct health services research, provide educational opportunities, develop research agendas responsive to regional and local needs, and render technical assistance." [19] VA hospitals were invited to work with their medical school affiliates in preparing these applications. When the university affiliate's center was funded, VA received enough support for a small unit (Table 19.2).

Table 19.2. Affiliations of VA hospitals with University Centers for Health Services Research* 1975-1981

University	Affiliated VA Hospital
University of California at Los Angeles	Brentwood
	Wadsworth
University of Washington	Seattle
University of Michigan	Ann Arbor**
University of Missouri	Columbia, MO**
Johns Hopkins University	Perry Point
University of North Carolina	Fayetteville
	Durham
University of Pennsylvania	Philadelphia
Yale University	West Haven**
Massachusetts Institute of Technology	Boston
University of Florida	Gainesville**

*The university centers were funded by the National Center for Health Services Research of the Department of Health, Education and Welfare.[19]

**These centers had Health Services Research Training Programs, funded by Education Service.

The staff of these units, assisted by their university affiliates, were then expected to apply for more research support from VA and other funding agencies. Four of these VA hospitals also received positions for trainees. While the program of the National Center for Health Services Research terminated after its initial five-year funding period, some of the VA-university partnerships established in these centers served as the basis for the VA Centers of Excellence in Health Services Research started in the 1980s.

Figure 19.3. Richard Greene, M.D., Ph.D.

In 1978, Evans recruited Richard Greene, M.D., Ph.D., to be a staff physician in HSR&D Service. Greene had been working with a group consulting in health services research and had most impressive credentials. Previously, he had been a Ph.D. molecular biologist in the NIH intramural program. In addition to his medical and scientific education, he held an M.P.H. from Johns Hopkins University. Not long after Greene arrived in 1979, Evans left for an intergovernmental detail to the National Academy of Sciences, and Greene became Director of HSR&D Service. A few months later, Vernon Nickel, M.D., the founding Director of Rehabilitative Engineering Research and Development Service, left for California to become a professor; Greene also served as Acting Director of that Service while a search was on for Nickel's replacement. Next, Betty Uzman left to go to the Memphis VA Hospital, and Greene became Acting Director of Medical Research, as well, later becoming permanent Director of Medical Research Service. Later in the 1980s, Greene became ACMD/R&D.

References

1. "Report of group in research in conjunction with committee on treatment and cure of veterans." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 230.

2. Interview with Mr. John Willoughby, May 4, 1992 at Mr. Willoughby's home.

3. Interview with Mr. John Peters, February 27, 1992 at Mr. Peters's office at the University of Alabama at Birmingham.

4. H. Martin Engle, M.D., "Memorandum No. 10-63-25. Committee on Administrative and Developmental Research." 8/14/63.

5. H. Martin Engle, M.D., "Memorandum No. 10-666-3. Administrative Research Committee." 2/25/66.

6. *VA Central Office Telephone Directory*. Washington, DC: 1967, 32.

7. Orin T. Skouge, M.D., "Circular 10-66-279. The Administrative Research Program." 12/22/66.

8. Benjamin B. Wells, M.D., "R&E Letter 65-2. Request for cooperation in research project." 2/26/65.

9. H. Martin Engle, M.D., "Memorandum No. 10-68-7. Abolishment of Administrative Research Committee." 4/4/68.

10. Orin T. Skouge, M.D., "RCS 13-109-5. Survey of Suggested Health Services Research and Development Projects." 7/8/69.

11. Adkins, R.E., "The Automated Hospital Information System", in *Medical Care of Veterans*. 1967, U.S. Government Printing Office: Washington, DC 390-391.

12. Interview with Lawrence Christianson, M.D., May 4, 1992 at Dr. Christianson's home in suburban Maryland.

13. Interview with Thomas Chalmers, M.D., July 29,1992 at a hotel lobby in Boston, MA.

14. Telephone interview with Orin Skouge, M.D., August 3, 1992.

15. Interview with Mr. Al Gavazzi, May 6, 1992 at Mr. Gavazzi's home in suburban Virginia.

16. Telephone interview with Walter Whitcomb, M.D., August 11, 1992.

17. Telephone interview with Mr. Harold (Jack) Divers, January 14, 1994.

18. Interview with Leon Bernstein, M.D., April 29, 1988 at Dr. Bernstein's home in suburban Virginia.

19. Kruegel, D. and Evans, C., "The organization of health services research in the Veterans Administration." *J Med Systems*, 1981. **5**: 157-162.

(Intentionally Blank)

Chapter 20. VA Research in Rehabilitation

Before the Oct. 1, 1973, establishment of the Research and Development Office, including Prosthetics Research, VA research in prosthetics and sensory aids was the responsibility of the clinical service that served Veterans who needed these devices. And only in 1976 did research in rehabilitation become a Service in its own right.

Post-war research guided by NRC committees

In the first 31 years after World War II, from 1945 to 1976, the National Research Council (NRC) of the National Academy of Sciences played an active role in encouraging and supporting research in prosthetics and sensory aids, both in VA and elsewhere. NRC committees reviewed proposals for contracts in support of prosthetics research, held meetings to review state-of-the-art prosthetics and advise on new directions, and interacted directly with contractors. Funds supporting contracts came from the Office of Scientific Research and Development (OSRD) and the War Department from 1945 to 1947; after that, VA provided the funding. Public Law 729, 80th Congress, June 19, 1948, formally authorized VA research in the fields of prosthetics and sensory devices and provided a budget of $1 million per year. The law required VA to "make available the results of such research so as to benefit all disabled people." The budget remained flat until 1962, when the $1 million funding ceiling was lifted by Public Law 87-572, which authorized "such funds as were necessary" for the program.[1]

Until the mid-1970s, the VA research program in prosthetics and sensory aids consisted primarily of contracts funded by VA, supervised by VA staff and reviewed by NRC committees.[2]

The NRC committee structure in support of this program changed from time to time (Appendix IIm), with shifts in the perception of needs and changes in the agencies (including VA) supporting research in prosthetics and sensory aids. NRC involvement began with a meeting to review the needs of amputees. The meeting, sponsored by the Army at the request of the NRC, was held at Northwestern University on Jan. 30-Feb. 1, 1945. One outcome of this meeting was a Committee on Prosthetic Devices formed by the NRC in April of that year. In October, the wartime OSRD transferred its Committee on Sensory Devices to the NRC. From then until 1975, the NRC continued to play a key role in guiding research in prosthetics and sensory devices, a large fraction of it supported by VA.

The 1945 meeting has been described as the beginning of modern research in prosthetics.[3] It was held just after the annual meeting of the American Academy of Orthopedic Surgeons in Chicago, and orthopedic surgeons were well represented by physicians including Henry Kessler and Paul Magnuson. The attendee representing the OSRD was Paul Klopsteg, Ph.D., Sc.D., a physicist at Northwestern University and Director of Research at Northwestern's Technological Institute.

Through subsequent reorganizations, these committees were guided in the early days by the Executive Director, Brig. Gen. F.S. Strong, Jr. An early assistant to General Strong was Eugene Murphy, who played a key role in the VA program.[4]

Eugene Murphy, Ph.D.

Dr. Eugene Murphy, himself paraplegic as a result of childhood poliomyelitis,[5] was a mechanical engineer. He spent World War II on leave from his graduate studies at the Illinois Institute of Technology teaching mechanical engineering students at the University of California in Berkeley and conducting research, supported by OSRD, on the stability of bonded wire in strain gages. These gages were used to measure the stretching of reinforcing bars in steel structures such as bridges and large ships.

Figure 20.1. Eugene Murphy, Ph.D.

Murphy was a friend of Howard D. Eberhart, B.S.E.E., professor of civil engineering at Berkeley, who lost a leg in a wartime research accident in 1944. Ironically, Eberhart had gained an interest in prosthetics research and knew the men he would come to work with in this field before the accident made him a user of the technology. Already acquainted with Murphy through professional engineering interests, he had been consulted by Verne Inman, M.D., an orthopedic surgeon at UC Medical School in San Francisco, concerning the biomechanics of the shoulder joint. After Eberhart's injury, Dr. Inman was his surgeon.

The accident that caused the loss of Eberhart's leg occurred while he was studying the stress on concrete from landing aircraft. While trying to develop more efficient reinforcing patterns for the concrete, to facilitate building longer runways for bombers with less material, he was run over by a trailer weighted to represent the landing gear of a B-29.

At the Mare Island Naval Hospital, under the guidance of Navy physician Henry Kessler—a leading expert in prosthetics—Eberhart was fitted with a conventional wooden foot and mechanical ankle joint prosthesis. In visits from Murphy, the two became interested in measuring the stresses involved in using this type of artificial leg. Back at the civil engineering laboratory in Berkeley, they rigged up various rudimentary measuring devices as Eberhart walked about as a test subject. Their research indicated strains on the prosthetic limb were far greater than initially supposed, and the two engineers realized that more sophisticated techniques were needed to measure the complexities involved in the dynamic motion of simple walking.[1]

Murphy described their experience to key people at the NRC, pointing out that little was really known about the mechanics of walking—knowledge critical to developing prosthetic lower limbs. The NRC officials were sufficiently impressed that Murphy became an assistant to Gen. Strong, helping to launch the NRC's initial effort in prosthetics research. Eberhart and Inman were given a contract for a formal research project, which endured for the next 35 years, leading to significant progress and understanding in the field of prosthetics.[4]

Prosthetics and Sensory Aids Service

In 1948, after Public Law 729 from the 80th Congress provided funding to VA in support of prosthetics research, Murphy moved from his staff job with the NRC to VA. Research in prosthetics and sensory aids in VA was administered by the new Prosthetics and Sensory Aids Service in VA Central Office. Its first Director was Augustus Thorndike, M.D., a prominent orthopedic surgeon at Harvard, who never moved to Washington. Dr. Thorndyke was well connected in the medical community, and he used his contacts in the American Medical Association, the American College of Surgeons, and other professional organizations to help raise the profile of VA's work in prosthetics and sensory aids. The Assistant Director for Operations, Robert E. Stewart, D.D.S., was based in the Central Office. After Thorndike retired in 1955, Dr. Stewart became Director, a position he held until he retired in 1973.

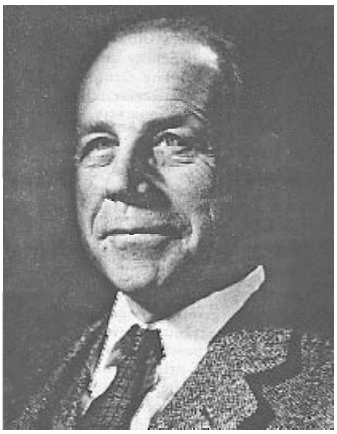


Figure 20.2. Augustus Thorndike, M.D.

Figure 20.3. Robert E. Stewart, D.D.S.

Murphy, as Assistant Director for Research, was based in New York City at the VA Regional Office. A "Prosthetics Testing and Development Laboratory" had been established in New York in 1945 by Walter Bura, who was in charge of VA's clinical prosthetics program from 1945 to 1948. This unit was independent of the NRC effort.

VA Prosthetics Center in New York

In 1955, Dr. Stewart, by then Director of the Prosthetics and Sensory Aids Service, visited the Sunnybrook Hospital in Toronto, where he learned about its prosthetics center that served 18 health centers throughout Canada and also engaged in research. He felt that a similar center would benefit VA. In 1956, he established the VA Prosthetics Center (VAPC) in New York. This Center combined a clinical operation with the research and evaluation effort already ongoing under Dr.

Murphy. Later, it established satellite stations at several VA hospitals.[6]

The research carried out at the VAPC constituted most of VA's intramural research in prosthetics and sensory aids before the 1973 reorganization that brought prosthetics research into the Office of Research and Development. While the VAPC carried out a variety of practical projects, primarily to improve upper and lower limb prostheses, it became increasingly involved in the evaluation of devices developed by others. It established a network of VA Prosthetics Service units at VA hospitals willing and able to evaluate new devices. In some cases, when the new device was clearly beneficial, it would be adopted in VA for general clinical use. The VAPC also played an active role in prosthetics education. Its activities were extensively discussed in the review of the prosthetics and sensory aids program by Stewart and Bernstock published in 1973[7] and were regularly reviewed in the *Bulletin of Prosthetics Research*.

Dr. Murphy's role

While he supervised the intramural research at the VAPC, Eugene Murphy's most important role was to coordinate the contracts program. Frank Coombs, who joined the program in the 1970s, described Murphy as a superb expeditor, the "bee in the flower garden, cross-pollinating things," who exchanged and furthered ideas. When he learned what one person was doing, he was quick to think of whom that person should confer with and would get them together, and then follow up.[4,8]

Bulletin of Prosthetics Research

A key contribution led by Murphy was the publication of information to be shared within the prosthetics and sensory aids community. From 1954 to 1972, with VA support, the NRC published a journal called *Artificial Limbs.* To cover the broader field of research included in its Prosthetics and Sensory Aids research program, VA started its own *Bulletin of Prosthetics Research* in 1964. Murphy continued as its editor until he retired in 1983.

The *Bulletin of Prosthetics Research* presented VA-sponsored research, both as progress reports and original articles, and also presented other research in the field. Recognized as a primary source of state-of-the–art information about research in prosthetics and sensory aids, by 1983 the *Bulletin* had expanded to include all areas of rehabilitation and changed its title to reflect its broader scope. Today known as the *Journal of Rehabilitation Research and Development*, this journal continues to expand and contribute to its field.

Early prosthetics research supported by VA

University of California at Berkeley

Work under the contract with UC Berkeley was begun even before VA took over funding of contracts in 1947. Researchers conducted classic fundamental studies on human locomotion, or gait analysis. Their early studies included limb and pelvis motion during locomotion and patterns of muscle activities in the lower limbs and trunk. To investigate these phenomena, they developed glass walkways and force plates. They used three-dimensional cinematography along with the force plates to greatly expand knowledge of human walking. This work had national and international

impact on the field of motion analysis. The team also performed materials testing and made studies of structural design that led to improvements in artificial-limb alignment and suction-socket design that reduced pain in amputee fittings. Later products completed under this long-lasting contract were the development of casting techniques and plastic laminates for sockets, improvement in the suction socket, a casting technique for total contact sockets for above-knee amputees, a patellar-tendon-bearing socket for below-knee amputees, a safety-lock knee and a

Table 20.1. Comparison of rehabilitation research projects funded in 1973 with those funded in 1980 [10, 11]
(1973 funding included where known [12])

Intramural projects active in 1973, terminated by 1980			
Orthopedics and prosthetics			
Moore et al	VAMC, San Francisco	Immediate postoperative prostheses	
McDowell	VAMC, Richmond	Immediate postoperative arm orthoses	
Spinal cord injury			
Davis	VAMC, Miami	Paralysis, spasticity and pain	
Extramural projects active in 1973, terminated by 1980			
Oversight			
McLaurin	Nat'l Academy of Sciences	Advisory committee	$167,000
Sensory aids			
Causey et al	University of Maryland	Hearing aid research	55,000
Carhart, Olsen	Northwestern University	Test proced, binaural hearing aids	
Benham et al	Bionic Instruments, Inc.	Laser cane for blind	35,000
Cooper et al	Haskins Laboratory, Inc.	Speech output- reading machine	134,400
Mauch, Smith	Mauch Laboratories	Reading machines	145,600
Weisgerber	Am. Inst. Res., Palo Alto	Training - Mauch Stereotoner	
Hathaway, Butow	Hadley School for Blind	Reading machine training	20,000
Orthopedics and prosthetics			
Mauch	Mauch Laboratories	Hydraulic limbs	110,000
Bennett	New York University	Evaluation of prostheses	20,930
Lyman et al	University of California, LA	Externally powered arm	49, 800
Sarmiento et al	University of Miami	Improved fitting procedure-leg	59,000
Graupe	Colorado State University	EMG-act contr for art upper arm	15,600
Perry	Rancho Los Amigos	Clinical gait analyzer	
Spinal cord injury			
Newell, Leavitt	Texas A&M Engineering	Automotive adaptive equip	
Scott	Mobility Engineering	Passenger safety, vehicle for handicap	
Perry, Allen	Rancho Los Amigos	Bed-chair	
Other			
Cochran	St. Lukes Hosp, NYC	Electrical stimulation of bone healing	
Chase, Babb	Univ Calif, LA	Lit search on electrode implantation	
Intramural projects active both in 1973 and 1980			
Orthopedics and prosthetics			
Burgess, Lippert	Seattle VAMC	Improved amputation and prostheses	
(Contract to University of Washington in 1973, Seattle VAMC in 1980)			
Sensory Aids			
Acton, De L'Aune	West Haven VAMC	Reading and mobility aids	
Malmazian, Farmer	Hines VAMC	Reading and mobility aids	
Hennessey et al	Palo Alto VAMC	Reading and mobility aids	
Other			
Schweiger, Lontz	Wilmington VAMC	Maxillofacial materials	

(Contract to Temple University in 1973, Wilmington VAMC in 1980)

Lee et al	Castle Point VAMC	Hemodynamic evaluation in amputees
Hoaglund et al	San Francisco VA	Lower limb prostheses, locomotion

(Contract to UC Berkeley in 1973, San Francisco VAMC in 1980)

Extramural projects active both in 1973 and 1980

Orthopedics and prosthetics

Thompson, Childress	Northwestern Univ.	Powered prostheses
Seamone, Schmeisser	Johns Hopkins	Ext powered arms, robots, wheel chair
Hall, Rostoker	Southwest Res Inst	Permanent artificial limbs

Intramural projects active in 1980, started after 1973

Rehabilitation Research and Development Centers

	Hines VAMC	Multidisciplinary program
Leifer	Palo Alto VAMC	Multidisciplinary program

Sensory Aids

Kelly	Atlanta VAMC	Wheelchairs, reading and mobility
Linvill et al	Palo Alto VAMC	Communication system for the blind

Orthopedics and prosthetics

Cochran et al	Castle Point VAMC	Electrical stimulation of bone transplants
Mears	Pittsburgh VAMC	Joint wear particles
Murray	Wood VAMC	Normal and abnormal motion
Marsolais	Cleveland VAMC	Engineering – Orthotics and prosthetics
Fortune, Leonard	Wash, DC VAMC	Grouting materials
Spadaro	Syracuse VAMC	Electrical stimulation of hard tissue
Cooper	Iowa City VAMC	Foot biomechanics
Lippert, Burgess	Seattle VAMC	Below-knee physiological suspension
Weinstein	New Orleans VAMC	Orthopedic implant retrieval
Golbranson	San Diego VAMC	Gait analysis
Malone et al	Tuscon VAMC	Postoperative prosthesis, arm and leg

Spinal cord injury

Perkash, Motloch	Palo Alto VAMC	Seating systems
Vistnes	Palo Alto VAMC	Pressure sores
Rossier	West Roxbury VA	Wheelchair – Myoelectric control
Weibell et al	Sepulveda VAMC	Wheelchair power steering
Bohlman et al	Cleveland VAMC	Spinal cord monitoring
Sypert, Munson	Gainesville VAMC	Spinal cord regeneration
Peckham	Cleveland VAMC	FES – upper extremity
Hussey, Rosen	West Roxbury VA	Muscle control by electrical stimulation

Other

Goldstein et al	Gainesville VAMC	Artificial larynx
Hood, Schoen	Gainesville VAMC	Lung reaction to biomaterials
Griffin, Schiavi	Nashville VAMC	Neuromuscular deficit techniques

Extramural projects active in 1980, started after 1973

Sensory Aids

Clark, Savoie	Telesensory Systems	Speech output for reading aid

Orthopedics and prosthetics

Swanson	Blodgett Med Ctr	Grommet bone liner
Banks	NASA Lewis Res	Finger joint grommets
Matsen	Univ. Washington	Neuromuscular structure viability

Spinal cord injury

Roemer et al	UC Santa Barbara	Bladder volume determination

pneumatic swing-control knee. Inman and Eberhart's work also resulted in the prosthetic foot that became the standard for its time, the Solid-Ankle Cushion-Heel (SACH) foot.[9]

Mauch laboratories

Another long-time contractor was Hans Mauch, who developed hydraulic swing-control knees and ankles and also worked on reading machines. Mauch had played a major role in developing Germany's V1 missile, and came to the U.S. with Werner von Braun.

Frank Coombs described Mauch as a "hydraulics wizard." He applied his expertise to the process of biomechanically replicating the motion of the human knee and ankle. The knee is far more sophisticated than a simple hinge; mechanically recreating its motion requires a variable center of rotation. Mauch's hydraulic configuration allowed the leg to swing forward normally during walking; then it would dampen its stopping point and suppress any backward motion. Mauch applied the same technology to the ankle joint by constructing a variable mechanical replica that adjusted to variations in up and down angles.[8]

University of California at Los Angeles

Another early contract that continued for many years was with UCLA. In the early years, the UCLA investigators collaborated with Northrup Aircraft, in Hawthorne, Calif. The UCLA-Northrup group did classic studies of upper-extremity motion comparable to those of the lower limb done at UC Berkeley. They identified the basic requirements for upper-extremity prostheses and developed improved models. But probably the UCLA group's most important contribution, which began in 1953 with VA prosthetics research funding, was a university-level prosthetics education course. This was soon followed by similar courses at New York University and Northwestern University. They taught up-to-date methods and worked to make prosthetics a profession. These programs, while not strictly centered on research, provided formal accreditation for prosthetists, a qualification that soon was required by VA for those who fitted Veterans with prosthetics.[13]

Northwestern University and the Rehabilitation Institute of Chicago

Northwestern University had been the cradle for modern prosthetics research, hosting the seminal 1945 meeting and providing the original NRC committee staff. In those early days, Northwestern had a contract for reviewing the literature and patents related to artificial limbs that led to a lengthy report on the state of the art. The University's researchers also worked on methods for testing artificial legs.

In 1954, largely as a result of the personal efforts of VA's Dr. Paul Magnuson, the Northwestern-affiliated Rehabilitation Institute of Chicago (RIC) was founded in the city's downtown. In 1958, a VA-sponsored Prosthetics Research Center was set up within the RIC. Its Chief was an orthopedic surgeon, Dr. Clinton Compere, one of the key professionals sustaining the new RIC. Dr. Compere, a combat surgeon in the South Pacific, had been chief of an Army amputee unit following WWII and knew Dr. Magnuson. The new program was charged with evaluating special amputation situations to facilitate the development and fit of appropriate devices. From its inception, the Prosthetics Research Program worked with the nearby Chicago Research VA Hospital, later called

the Chicago Lakeside VA Medical Center, drawing clinical collaboration from the VA hospital as well as from its host, the RIC.

A wide variety of prosthetic devices were developed at the Northwestern unit. Early on, its engineers became interested in use of external power in prosthetics. In 1966, electrical engineer Dudley Childress, Ph.D., joined the staff. In 1968, he and his associates fitted the first self-contained and self-suspended trans-radial myoelectric prosthesis. With this system, which later became commercially available, the amputee activates the same muscles that had controlled the original arm. Electrodes on the skin then pick up the muscle activation signal which is electronically amplified to control small motors in the artificial arm. The first person ever fitted with such a device later became a successful New York banker who also used later generations of the myoelectric hand. A large cadre of individuals were fitted in this way in Chicago, and they provided design feedback to Childress and his team.

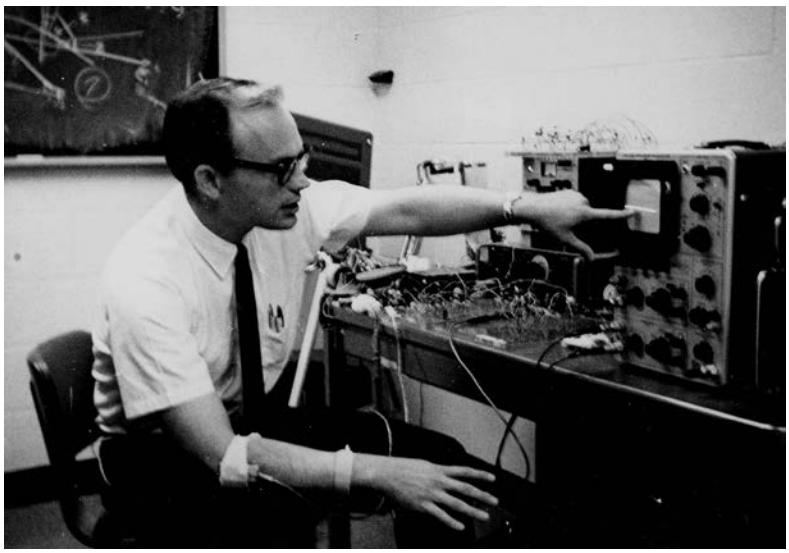


Figure 20.4. Dudley Childress, Ph.D.

The Prosthetics Research Laboratory, attached to VA Lakeside Hospital, became known world wide for practical and elegant myoelectric systems. VA held a national educational course at Northwestern University's prosthetics school in the early 1970s, enrolling approximately 50 students, where VA clinicians learned how to fit the new prostheses. This event launched myoelectric prosthetics for American Veterans. Subsequently, Childress designed a new prehension mechanism that used two motors acting in synergy. Thirty years later, the principle was still employed in three commercially available prosthetic systems. The Myo-Pulse modulation scheme that Childress created for the myoelectric signal processor was revolutionary because of its high performance and simplicity of design. The modulation principle, which essentially eliminates delays in the electronics, enables a prosthesis to respond instantly to its wearer's wishes.

Childress and John Billock were successful using the Northwestern socket that Billock designed for people with trans-radial amputations. They also had success with transhumeral amputations by using a body-powered elbow and myoelectric hand controlled with a myoelectric signal from the biceps and

triceps brachii. This fitting method is standard today in VA and civilian prosthetics facilities. The team also developed a multi-state myoelectric arm that allowed the biceps and triceps to control four degrees of freedom of the arm.

Childress and his team at the RIC Prosthetics Research Center were also leaders during the 1970s and 1980s in the development of many rehabilitation-engineering systems for people with spinal cord injuries. They were the first to design and commercially introduce the "sip and puff" wheelchair controller for those with high-level quadriplegia. Ms. Margaret Pfrommer, who had significant quadriplegia, had a 25-year tenure in their laboratory as a laboratory assistant. The group developed a wide range of assistive equipment for persons with similar significant disabilities. Such equipment is now common and much advanced, but during the 1970s and early 1980s very few devices of this kind were available. Ms. Pfrommer used the "sip and puff" wheelchair, and the Childress team designed many devices around this control concept. Items developed and marketed through a national company included the first solid-state environmental control system for office and/or home and the first dedicated computer (in 1973) that allowed a person to serve as a receptionist and office assistant. Pfrommer demonstrated the effectiveness of this equipment in her home as well as in the laboratory. Her home was adapted so that she could live alone, with caregivers needed only in the morning and evening. Childress integrated her rocking bed with a positive pressure ventilator. She became a strong advocate for technology in rehabilitation and was a compelling spokesperson and example for what persons with disability could do if given the proper tools.[14, 15]

University of Washington: The Prosthetics Research Study, Seattle

In 1964, Ernest Burgess, M.D., an orthopedic surgeon in Seattle and Chief of the amputee clinic at the Seattle VA Hospital, organized a VA-sponsored study of the theoretical and practical aspects of Immediate Postsurgical Prosthetic Fitting (IPPF). This technique had recently been described by a Polish surgeon and professor, M. Weiss, M.D. On hearing about Professor Weiss's work, Burgess organized a national workshop of VA clinic team directors and other leaders in the prosthetic and amputee rehabilitation field to review this new technique. After the workshop, VA funded Burgess and his co-workers to undertake a clinical investigation. A laboratory was established at the Pacific Northwest Research Center, and the clinical base for the program was centered on the Seattle VA Hospital campus but involved all of the hospitals affiliated with the University of Washington.

The first cases of IPPF, patients cared for by a team with Dr. Burgess as the surgeon, were successful. Within a few months, it had become apparent that these patients had less postoperative pain and their rehabilitation was faster than in the past. However, it also became clear that many areas called for further research. In subsequent years, this group studied surgical and casting techniques, materials, wound healing, measurement of tissue circulation, selection of amputation site and many related issues. It redefined the surgical procedure of amputation as a part of the rehabilitation procedure and introduced a new family of surgical reconstruction techniques and a series of new prosthetic devices.[16]

During the 1980s, collaborating with engineers at Boeing Aerospace, Burgess's laboratory developed the Seattle Foot system, incorporating light-weight, responsive materials that capture an amputee's natural movement. Dr. Burgess is personally credited with having strongly advocated one particularly distinctive attribute of the system: an energy saving and return feature. As the

wearer brings the foot down, the structure absorbs and briefly stores excess energy from the downward momentum; as the wearer begins lifting the foot for the next step, the stored energy is released to spring the foot up, giving the wearer a positive sense of "pushing off."[17]

Combining this system with computer-aided design and manufacture, the Seattle group developed a method for producing better-fitting prostheses more quickly and inexpensively than was possible before. This system, the CAD-CAM system, is now being used widely in VA and elsewhere. It is being used successfully to provide inexpensive and comfortable limbs for amputees in Vietnam and other countries that have been ravaged by land mines from recent wars.[18]

Sensory aids research

The need for improved care of those who became blind or deaf as a result of their military service concerned the wartime Committee on Medical Research of the Office of Scientific Research and Development. In January 1944, the OSRD formed a Committee on Sensory Devices. This Committee was transferred to the NRC in October 1945, when the OSRD closed down its operations. In 1950 the Committee sponsored a book titled *Blindness: Modern Approach to the Unseen Environment* that reviewed the state of the art in assistive technology for limited vision. In a 1954 NRC reorganization, this committee was dissolved and its activities ceased. The NRC did not review or support sensory aids research for the next 10 years. In 1964, at the request of VA, the NRC established a new Subcommittee on Sensory Aids under its Committee on Prosthetics Research and Development.[19] Administration of sensory aids research in VA was part of the prosthetics research program, led by Eugene Murphy in the New York office during the entire period leading up to, and for several years after, the 1973 reorganization of VA. While some contracts related to hearing aids were consistently in the portfolio, the effort was focused on blindness.

VA's specialized care of the blinded Veteran began with establishment of the first Center for Rehabilitation of the Blind at the Hines VA Hospital in Chicago. In this program, selected blind Veterans were trained in a variety of skills.[20] This Center, and the Blind Centers later established at the Palo Alto and West Haven VA Hospitals, provided VA with a focus, as well as willing participants, in efforts to improve life for Veterans and others with severe visual impairment..

Mobility aids for the blind

Development of an effective obstacle detector to help blind persons navigate has long been a challenge. VA began supporting research directed to this problem in the 1940s.

In 1948, VA bought 25 "Signal Corps Devices," single-channel obstacle detectors built by RCA. VA contracted for their evaluation with Thomas A. Benham, a blind faculty member at Haverford College. Professor Benham reported on his results and suggested improvements in a 1952 report. In 1953, VA contracted with Haverford to allow Benham to oversee development of an improved device. Haverford subcontracted work to a commercial firm, Bionic Instruments. Over the next 16 years, under VA contract, 10 devices were developed, ultimately including practical laser canes for the blind. The 1975 product, the C-5 Laser Cane, emitted three pulses of infrared light, directed up, down and straight ahead. The light is reflected from an object in front of it and detected by a

photodiode placed behind a receiving lens. The angle made by the reflected ray passing through the lens indicates the distance of the object detected. The cane makes a sound when the downward beam detects a drop-off or the upward beam detects an overhead barrier. Sounds of different frequencies indicate the barriers ahead, in front of and above the user. VA developed the training programs necessary for proper use of this device. It proved to be appropriate only in certain circumstances, for highly motivated users and for training of the newly blind, who later were able to maneuver without it. The cost and skills required were substantial, but they were less than those needed for use of a guide dog.[21]

Reading machines

The early contracts from the NRC supporting research on reading machines for blind Veterans involved attempts to translate printed material to sound. This work ended in 1954 when the Committee on Sensory Devices was dissolved.[22] Between 1954 and 1958, VA and NRC sponsored a series of five conferences for people interested in further development of reading machines, but there was essentially no governmental support of research to advance the field during that period. These conferences attracted wide attention: from 11 attendees at the first conference in 1954 to 68 at the fifth in 1958. Despite the lack of funding, the conferences stimulated new ideas.[23]

In 1957, VA started a funded program to develop reading machines for those with severe visual impairment. The earliest product of this new program was the improved Optophone, developed at Battelle Memorial Institute by upgrading and transistorizing a device developed in the 1940s by RCA. This device translated the printed word into a series of nine tones representing portions of the letters in each word. Five prototypes were produced and a group of blind students and adults learned to use it. Several blind VA employees became experts in its use, but reading was very slow. The Battelle device was never widely distributed, but led to other more widely accepted devices.[24]

In the Mauch Laboratories, in addition to the prosthetics development described earlier, Hans Mauch started a reading machine project in 1957 that lasted 20 years. His first contract from VA was to contribute to the Batelle Optophone. His first assignment: to develop an improved tracking device, which he called the Colineator. Soon, Mauch and his colleagues were working on a machine that produced speech-like sounds in response to letter shapes. When this did not prove practical, Mauch moved to the use of recorded phonemes based on letter shapes, using the "spelled speech" system being developed under VA contract by Professor Milton Metfessel of the University of Southern California. This "Cognodictor" went through a number of modifications leading to a field prototype delivered in 1969 and to further improvements up until 1976.

Meanwhile, Mauch was also developing a hand-held probe that gave tactile responses to letters, a device called the Visotactor. It was like a miniature version of the Optophone, except that its output was tactile rather than auditory. Mauch then changed the output to a system of sounds instead of the tactile output, producing the Visotoner. The Visotactor, Visotoner and Optophone were all practical for reading when used by well-motivated, thoroughly trained and intelligent blind users. At best, however, reading was slow. Mauch continued to improve these small, relatively inexpensive "direct translation" devices and in 1972 produced the Stereotoner, which took advantage of a double array of detectors to speed the letter recognition process by producing its tones binaurally. The Visotactor, Visotoner and Stereotactor were originally intended to be useful components in the

development of the Cognodictor. In fact, in the hands of trained users, they were more practical when used directly; they continued to be used by a few blind readers, while the Cognodictor never entered the practical-use phase of development.[25, 26]

Franklin Cooper of the Haskins Laboratory in New York (and later in New Haven, Conn.) and his colleagues had worked on the reading machine concept in the 1940s under the Committee on Sensory Devices. They had developed a device that produced a tone pattern in response to the shapes of letters. However, Cooper's interest had turned more and more to the problem of production of standard English, and the laboratory conducted fundamental linguistic research toward that end. When VA started funding its reading machine program in 1957, Haskins received a contract to produce "audible outputs of reading machines for the blind." For a shorter-range product, they had a second contract for an interim device—a reading machine that could recognize a vocabulary of up to 7,200 words. Since optical character recognition was not yet developed, for input they used a punched-tape system from the printing industry. Ability to read these tapes would, in principle, make a wide variety of printed material accessible to blind persons. The short-range project never reached the clinical testing phase, but the long-range project, production of synthetic speech from the written word, led to important theoretical advances.

Mauch's group developed a system of linguistic rules to synthesize speech, leading to their primary product, Speech Synthesis by Rule. Eventually, in 1973, they produced a prototype reading machine that provided a version of synthetic speech. It depended on a commercially available optical character reader and on four Haskins developments: a text-to-phoneme dictionary look-up, stress and intonement assignment, Speech Synthesis by Rule, and a parallel resonance synthesizer. Editorial corrections were needed at several points in the process. While a usable reading machine did not result from the many years of research that the Haskins Laboratory carried out with VA funding, the basic knowledge gained was important to the ultimate development of a practical reading machine in the mid-1970s.[27, 28]

VA was active in reading machine development until 1978, but none of the devices developed under VA contract was ultimately successful in the market. The first commercially successful devices were the Optacon, a tactile Braille-like instrument using air jets, developed by James Bliss, Ph.D., and John Linvill, Sc.D., at Stanford Research Institute and Stanford University, and the Reading Machine of Dr. Raymond Kursweil, Ph.D., which produced electronic speech in response to text. The Optacon was a direct competitor for the Stereotoner, and comparative testing showed both to be useful. However, the Optacon was marketed and the Stereotoner never reached the open market even though it was less expensive.[29]

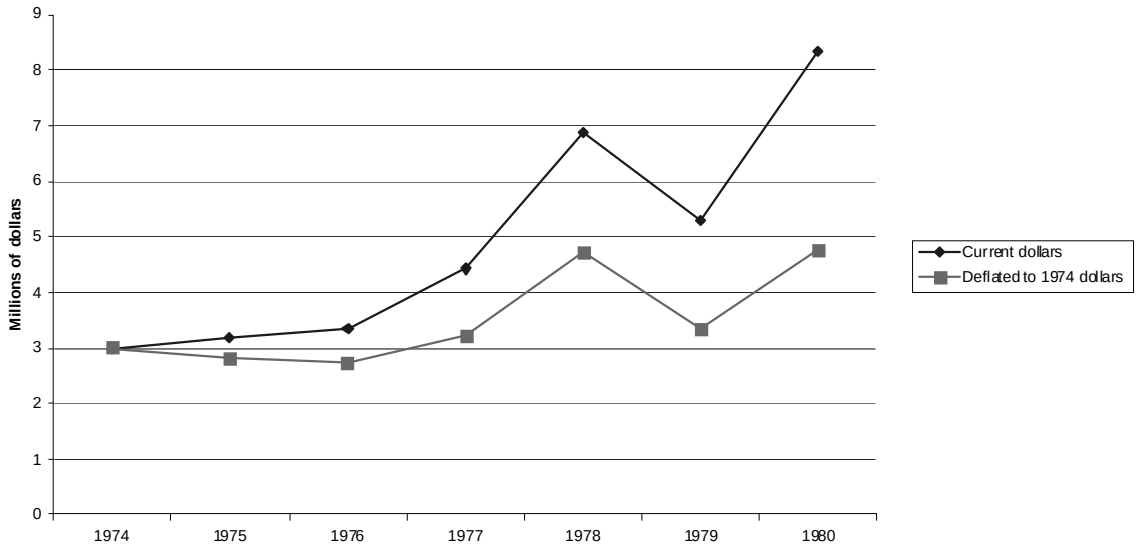
Though they were not themeselves initially funded by VA, the successful developers of reading machines benefited from the work that had been done under VA contract. The Kurzweil machine took advantage of the linguistic knowledge gained in the basic research done by the Haskins group. Both the Optacon and the Kurzweil Reading Machine were evaluated in VA's Blind Centers. Linvill, in fact, was a coinvestigator of a VA intramural project at the Palo Alto VA Medical Center's Blind Rehabilitation Center during the late 1970s,[30] and Bliss and Linvill's company, Telesensory Systems, Inc., had a VA contract in 1980 to develop a speech output for the Optacon.[31] All of the important devices designed to assist blind persons in reading have been tested and compared in VA Centers.[32]

Emergence of a new Rehabilitation Engineering R&D Service, 1973–1980

When VA reorganized its research and education program in 1973, setting up the new Office of Research and Development with Thomas Newcomb, M.D., as the first ACMD/R&D, the old Prosthetics and Sensory Aids Service was divided. Its clinical responsibility remained in the Professional Services, its training activities became a part of the Academic Affairs program and its research and development became a Prosthetics Research Program in the new Office of Research and Development. At that time, Dr. Stewart, who, as Director of the Prosthetics and Sensory Aids Service had taken an active interest in the research program, retired. Dr. Murphy and the VA Prosthetics Center remained in New York, but the center of research administration for the program moved to Washington. Thomas Radley, M.D., Assistant Director of Surgery Service in Central Office, became the Acting Director of the new Prosthetics Research Program under Dr. Newcomb.[33]

Newcomb believed that VA research in rehabilitation needed increased status and support and that these could be gained if the program were administered by a separate Service in the R&D Office. He gained the support of the Veterans' service organizations that were especially interested in people with disabilities and of others in VA Central Office.[34] His effort was rewarded when, in 1976, the Prosthetics Research Program was given Service status and renamed the Rehabilitation Engineering Research and Development Service.[35] This new designation reflected the understanding that research needs in rehabilitation transcended the scope of prosthetics and sensory aids alone.

Figure 20.5 Rehabilitation Engineering R&D budget, 1974-1980



Budget increases

The new Service, set up with congressional approval and with a new mission, was rewarded with more money to spend. The Veterans' service organizations were enthusiastic about the new direction, and the national climate favored improving the lot of people with disabilities.
The 1947 congressional appropriation of $1 million for the VA Prosthetics Research program had not been increased at all by 1976, after inflation was taken into account. Now VA requested and received additional money to support its new effort. Between 1976 and 1980, the Rehabilitation Engineering R&D Service's congressional appropriation had more than doubled. Even taking into account the high rate of inflation in those years, this four-year increase was substantial (Figure 20.5) and made it possible to move in new directions.

Program moves from contracts to intramural research

By the late 1970s, things were very different in VA than they had been when the contractual prosthetics research program began in 1947. Medical Research had become a vigorous intramural program, recognized widely as beneficial to VA's Veteran patients. Newcomb and his colleagues were convinced that VA would benefit more from an intramural program of rehabilitation research than from a purely contractual program. It was also believed that VA patients were more likely to receive direct benefits if the research was done in VA hospitals. A major policy change was agreed upon: In the future, where possible, VA research funds for rehabilitation research would be allocated to VA investigators.[34] When feasible, the contracts that remained would be supervised by a VA investigator and assigned to a VA medical center.[8]

By 1980, the majority of the research supported by VA Rehabilitation Engineering R&D budget was either carried out in VA hospitals or involved VA staff (Table 20.1).

VA forms its own peer-review system for rehabilitation research

From its inception, peer review for the VA rehabilitation research program was by the NRC's Committee on Prosthetics Research and Development (CPRD). By the mid-1970s, change was desired.[8] Although the Committee's membership rotated regularly, it became difficult to find qualified members with no conflicts of interest, and reappointments were frequent. In 1975, Newcomb offered a contract to NAS to review the activities of its CPRD. The Academy declined the contract, and the following year, by mutual agreement, the CPRD disbanded.[34]

This left VA with a need for a peer-review mechanism for its rehabilitation research program. At first, Dr. Murphy supervised the review process from his New York base, primarily using ad hoc written reviews. But by this time, both Medical Research Service and Health Services R&D Service had systems of Merit Review Boards meeting regularly to review proposals. In 1976, the new Rehabilitation Engineering R&D Service held its first Merit Review Board meeting.[8]

First two Rehabilitation Engineering R&D Centers

To create an academic base to boost VA rehabilitation research, Newcomb and his advisors decided to set up Centers of Excellence in Rehabilitation Research at VA hospitals that had close affiliations with schools of engineering. In 1976, Dr. Chase, the Chief Medical Director, signed a Request for Proposals sent to all VA hospitals describing the criteria envisioned for such Centers:

"a. Close proximity to and preferably location on premises of a VA health care facility with substantial clinical programs in important areas of rehabilitation, e.g., spinal cord injury, blind rehabilitation, amputee clinic, geriatric medicine, maxillo-facial restoration, prosthetics and orthotics clinics, etc.

b. Ready access to engineering expertise preferably from a major academic institution.

c. Close proximity to a medical school.

d. Association with allied health schools such as physical and occupational therapy with expertise in electromyography, biomechanics, kinesiology, etc."[36]

A committee of experts reviewed the applications and site-visited the leading candidates. The application from the Hines (Ill.) VA Medical Center, in affiliation with the Illinois Institute of Technology, received the committee's highest recommendation. In second place was the application from the Palo Alto (Calif.) VA Medical Center and the Stanford School of Engineering. Since only one Center could be approved, in 1977 Hines was awarded the first Center, together with support for renovation of space and funds to hire a cadre of investigators and support staff. Soon, however, Palo Alto was also funded for a Rehabilitation Engineering R&D Center.[34]

Rehabilitation Engineering R&D Service recruits its first Director

Shortly after Rehabilitation Engineering R&D became a Service, the search for a Director began. Vernon Nickel, M.D., from Ranch Los Amigos Hospital in Downey, Calif., near Los Angeles, became intrigued with the potential of the new Service and eventually accepted the Directorship in late 1977. He saw the appointment as an opportunity to "build something new," and he approached it with great enthusiasm.[17]

Figure 20.6. Vernon Nickel, M.D.

Frank Coombs, an engineer who had joined the Service a few months before Nickel arrived, served as Nickel's assistant. Coombs was an organized person capable of making changes smoothly. He and Nickel had complementary talents that made for an effective start of the new organization.

Nickel traveled extensively, meeting with VA investigators and with others interested in the program. He took seriously the responsibility to expand the program beyond the limits of

prosthetics and sensory aids. Under his leadership, the program grew and became more and more intramural. It also began to encompass extensive work in the rehabilitation of spinal cord injury, including development of robotic "servants" for the severely paralyzed, improved wheelchairs, electrical stimulation of paralyzed muscles and prevention of pressure sores. New programs began in restorations for people with mutilating facial deformities and for those with loss of the larynx. A number of more basic rehabilitation-related research programs were also started. (Table 20.1).

In 1979, the Rehabilitation R&D Service joined with Medical Research Service in identifying tissue regeneration as a high-priority research area. Basic research in regeneration was encouraged, as well as more attempts to apply current science to achieving regeneration, especially of nerves and the spinal cord. The first of a series of conferences, organized by Medical Investigator Robert Becker, an orthopedic surgeon who used electrical stimulation to enhance bone healing, was held in Syracuse NY in 1979. Attendees reviewed the state of the art and recommended that VA undertake an organized effort in this area. Tissue regeneration has since been a long-term VA research priority, still supported by the two Services.

During 1980, Dr. Nickel left Central Office to return to the West Coast. The new Service was beginning to grow and flourish. In 1983, its name was simplified, and it is now the Rehabilitation R&D Service. Later Directors have encouraged the growth that began in the 1970s and have continued to guard the quality of VA-supported rehabilitation research.

References

1. Stewart, R. and Bernstock, W., *Veterans Administration prosthetic and sensory aids program since World War II*. Washington, DC: U.S. Government Printing Office, 1977, 66.

2. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 31-109.

3. Interview with Dudley Childress, Ph.D., April 8, 2001 at Dr. Childress's home in Wilmette, IL.

4. Interview with Eugene F. Murphy, Ph.D., October 29, 1992 at Dr. Murphy's home in New York, NY.

5. Childress, D., Ph.D., "Eugene F. Murphy (1913-2000): Polymath of prosthetics." *Capabilities*, 2001. **10**: 1-2.

6. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 125.

7. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977.

8. Interview with Frank Coombs, May 4, 1992 at the RRD Office in Washington, DC.

9. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 34-41, 70-74.

10. Nickel, V.L., "Veterans Administration rehabilitative engineering research and development programs." *Bulletin of Prosthetics Research*, 1980. **17**: 65-143.

11. Murphy, E.F., "Highlights of other VA research programs." *Bulletin of Prosthetics Research*, 1974. **11**: 109-173.

12. Letter from Director, Prosthetic and Sensory Aids Service to Director, Supply Service, 1/30/73.

13. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 51-52, 91.

14. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 86-87.

15. Childress, D., Ph.D., personal communication with author, February 6, 2002.

16. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 93-96.

17. Interview with Vernon L. Nickel, M.D., January 15, 1992 at a restaurant in San Diego, CA.

18. Interview with Ernest Burgess, M.D., November 4, 1992 at Dr. Burgess's office in Seattle, WA.

19. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 30-31.

20. Haugen, J.S., *Reading Machines for the Blind: A study of Federally supported technology development and innovation, 1943-1980*. Blacksburg, VA: Virginia Polytechnic Institute and State University, 1995, 47.

21. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 102-104.

22. Haugen, *Reading Machines for the Blind*. 1995, 13-20.

23. Haugen, *Reading Machines for the Blind*. 1995, 50-54.

24. Haugen, *Reading Machines for the Blind*. 1995, 62-68.

25. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 98-100, 105-109.

26. Haugen, *Reading Machines for the Blind*. 1995, 69-97.

27. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 104-105.

28. Haugen, *Reading Machines for the Blind*. 1995, 98-118.

29. Haugen, *Reading Machines for the Blind:*. 1995, 8.

30. Nickel, V.L., "Veterans Administration rehabilitative engineering research and development programs." *Bulletin of Prosthetics Research*, 1980. **17**: 113-115.

31. Nickel, V.L., "Veterans Administration rehabilitative engineering research and development programs." *Bulletin of Prosthetics Research*, 1980. **17**: 111-112.

32. Telephone interview with Gregory Goodrich, Ph.D., January 29, 2002.

33. Stewart and Bernstock, *VA prosthetic and sensory aids program*. 1977, 3-4.

34. Interview with Thomas Newcomb, M.D., March 29, 1992 at a hotel lobby in Washington, DC.

35. Chase, J.D., M.D., "IL 10-76-2 Chief Medical Director's Letter. Rehabilitation Engineering R&D Service." January 20, 1976.

36. Chase, J.D., M.D., "IL 10-76-40 Chief Medical Director's Letter. Rehabilitative engineering research and development center." August 5, 1976.

Epilogue, 1981-2010

The VA research and development program continued to evolve after 1980. Today, under the leadership of Joel Kupersmith, M.D. , who has been VA's Chief Research and Development Officer since July 2005, VA's Research and Development program is an acclaimed model for conducting superior bench-to-bedside research. As it has long been, the Office of Research and Development (as it is now called) still serves as a model of research excellence, fully integrating fundamental, clinical and applied research.

VA continues to attract exceptional investigators and fosters dynamic collaborations with other federal agencies, academic institutions, and private industry. The Career Development Program for researchers, whose origins are described in this book, continues to accelerate the development of top-caliber investigators; VA's Cooperative Studies Program still thrives; and the peer-review program, the subject of past controversy, ensures all VA research meets the highest standards of scientific excellence.

Among the accomplishments of VA researchers since 1980 have been the development, in 1984, of the nicotine patch; the demonstration that one aspirin tablet a day reduced the rate of heart attacks; the identification, in 1994, of a gene associated with a major risk for schizophrenia; the invention of the first powered ankle-foot prosthesis in 2007; the largest ever clinical trial of psychotherapy to treat post-traumatic stress disorder, launched in 2003, and the largest health study ever of Vietnam-era women Veterans, begun in 2009. Also in 2009, VA's Clinical Research Pharmacy Coordinating Center, in Albuquerque, New Mexico, was named one of the five recipients of the 2009 Malcolm Baldrige National Quality Award, the nation's highest award for organizational excellence. The Center manages the devices and pharmaceuticals that are used in research trials conducted within the VA health care system.

Today's Office of Research and Development is a leader in conducting comparative effectiveness research—head to head studies that help clarify which among two or more health interventions works better for a given health condition in certain patients. VA has instituted a technology transfer program, which helps VA researchers commercialize their inventions. A Quality Enhancement Research Initiative (QUERI), started in the late 1990's, facilitates the clinical use of treatments, tests and models of care that are supported by research evidence.

Personalized medical research, tailoring health care treatment programs to individual patients, is a subject of great interest to many VA researchers, as is the new science of Genomics—the study of a person's genetic information to help tailor therapies to each person's genetic makeup. As this book goes to press in early 2010, VA is about to begin the process of collecting genetic specimens from 1 million veterans. These samples will help the Department to optimize medical care for veterans; enhance the development of tests and treatments for relevant diseases, and examine the potential of emerging genomic technologies.

Today's VA has put rehabilitation research on a true scientific footing by adding basic science in finding solutions to the needs of veterans with disabilities. There are now thirteen Rehabilitation Research and Development Centers of Excellence, including a center for brain rehabilitation research; one for limb loss and prosthetic engineering; one for the restoration of nervous system

function, and a rehabilitation outcomes research center, which evaluates rehabilitation programs and interventions that result in optimal patient outcomes.

For the future beyond 2010, VA Secretary Eric K. Shinseki has established thirteen challenges the Department faces as it transformed into a high-performing organization that is better aligned with 21st century veterans and their needs. Among them is to "Perform Research and Development to Enhance the Long-Term Health and Well-Being of Veterans." The Secretary intends for VA research to continue to play a leading role in the advancement of clinical medical knowledge, particularly in health issues associated with military service, by excelling in research and development of evidence-based clinical care and delivery system improvements to enhance the long-term health and well being of veterans. It is a path the Office of Research and Development is well prepared to follow.

Since 1980, the Office has continued to cope with competition for funding. Its leaders rely more and more on the Merit Review process to make difficult decisions among programs. Increasingly, the criterion for supporting projects has become scientific merit as determined by peer review, with less emphasis placed than in the past on assuring the continuity of the programs of established VA investigators.. By the end of the 1980s, a "pay line" was in place for all of the R&D programs, so that even a program a peer review group approved as meritorious would not be funded unless it had received a high priority score. While the Research Advisory Group continued to provide funding for new researchers into the 1990s, it became harder and harder to get funding through that source, and the program was eventually abandoned.

Medical Research Service's Career Development Program continued to be very prestigious, but funding limitations in the 1980s and 90s made awards increasingly difficult to obtain at that time. Health Services R&D Service added its own Career Development Program in 1991, and it has nourished an important cadre of young health services researchers. Eventually, in the late 1990s, the Career Development Program was restructured to serve primarily junior applicants and to include appointments in all areas of Research and Development. The Medical Investigator and Senior Medical Investigator Career Development levels, designed for established investigators, were discontinued.

In the mid-1990s, the Cooperative Studies Program became a freestanding Service, and Cooperative Studies support became equally available to projects in Medical Research, Health Service Research and Development (HSR&D), Biomedical Laboratory Research and Development (BLR&D) and Rehabilitation Research and Development (RR&D.)

VA's Research and Development program continues to be an essential part of the Department's mission to provide cutting-edge health care to America's veterans. Based on its past accomplishments, the "jewel in the crown" of VA health care will shine brightly for many years to come.

Appendices

(Intentionally Blank)

Appendix I. Middleton Awards, 1960-1995

Awardee	Medical center	Citation
1960 Solomon Berson, M.D Rosalyn Yalow, Ph.D.	Bronx Bronx	For showing that injected insulin is capable of inducing an immune response which can be quantitated.
1961 Hubert Pipberger, M.D.	Wash, DC	For pioneering the computer processing of the electrocardiogram.
1962 Leslie Zieve, M.D. William C. Vogel	Minneapolis Minneapolis	For studies of phospholipids and phospholipases.
1963 Stanley Ulick	Bronx	For his work in the chemistry and metabolism of mineralocorticoid hormones.
1964 Robert O. Becker, M.D.	Syracuse	For his identification of electrical control systems in living organisms, including man.
1965 Lucien Guze, M.D. George Kalmanson, M.D.	LA Wadsworth LA Wadsworth	For discerning the host-parasite relatinship in chronic, infectious kidney disease.
1966 Leo Hollister, M.D.	Palo Alto	For numerous, signifiacnt contributions in the field of therapeutic drugs for mental illness.
1967 Leonard T. Skeggs, Ph.D.	Cleveland	For automated laboratory test devices and biochemistry of hypertension.
1968 Thomas Starzl, M.D.	Denver	For pioneering surgical transplantation of kidneys and other human organs, including the development of anti-lymphocyte serum and globulin to suppress the rejection of transplanted organs.
1969 Roger Unger, M.D.	Dallas	For his conception of the physiology of metabolism of fats and carbohydrates, better to better therapy for diabetes patients.
1970 Andrew V. Schally	New Orleans	For his investigations of the physiology and biochemistry of hypothalamic neurohormones.
1971 Marcus Rothschild, M.D.	New York	For basic and clinical research on the pathological biochemistry of the liver in alcoholism and other types of liver disease.

1972 Kenneth Sterling, M.D.	Bronx	Developed the 51-Cr-labelling of erythrocytes for in vivo study as a clinical tool; first to use labelled human serum albumin for determinations of rates of turnover of this molecule in man and first to use 131-I-labelled thyroxine and triiodothyronine to study the disposal and turnover rates of these hormones in man.
1973 Ludwig Gross, M.D.	Bronx	For demonstrating viral etiology of leukemia in mammals.
1974 Paul Srere, Ph.D.	Dallas	Biochemical accomplishments on key cellular metabolic pathways regulating lipid and carbohydrate synthesis and storage.
1975 Paul Heller, M.D.	Chicago WS	Research in hematology, immunology, enzymology and metabolism, including findings on the mechanism of immunologic deficiency in multiple myeloma, a form of cancer.
1976 William Oldendorf, M.D.	Brentwood	Development of nuclear techniques in clinical neurology; the first description of computerized tomography; development of techniques of cerebral blood flow measurement; elaboration of cerebrospinal fluid functions; and characterization of blood brain barrier permeability.
1977 Charles Lieber, M.D.	Bronx	Toxicity of alcohol, elucidation of its interaction with drug, lipid and uric acid metabolism, and the pathogenesis of fatty liver and cirrhosis in man and subhuman primates.
1978 Victor Herbert, M.D.	Bronx	Developing scientific tools to diagnose nutrient deficiencies, measure nutrient binding proteins, demonstrate selective deficiency of nutrients in one cell line but not another, and applying the scientific criteria of safety and efficacy to nutrition folklore.
1979 Edward Freis, M.D.	Washington, DC	Studies of hypertension that proved the efficacy and life saving qualities of medical treatment.
1980 Norman Talal	San Francisco	For the development of immunologic concepts derived from the study of patients and animal models for autoimmune and malignant disorders, and for exploring

			the interface between the immune and endocrine systems which has led to new theoretical and therapeutic considerations for human diseases.
1981	Sami I. Said	Oklahoma City	For his contributions to the understanding of metabolic and endocrine aspects of lung disease, and for his discovery and characterization of vasoactive intestinal peptide (VIP).
1982	Abba J. Kastin	New Orleans	For his contributions to neuroendocrinology and for pioneering work with brain peptides, characterized by the many aspects of his concept of their multiple, independent actions.
1983	(2 awardees)		
	Norman H. Bell	Charleson, SC	For contributions to the basic science of hormone secretion and mineral metabolism and for delineating the metabolism of Vitamin D in normal and disease states.
	Sydney Finegold	LA Wadsworth	For firmly establishing the importance of anaerobic bacteria in infections of all types; describing the clinical picture and unique features of such infections; developing simple, rapid methods for diagnosing anaerobic infections; and for laboratory and clinical studies leading to effective therapy of these infections.
1984	Kosaku Uyeda	Dallas	for contributions in the field of carbohydrate metabolism and biochemical mechanisms of enzyme action.
1985	Albert L. Jones, M.D.	San Francisco	For contributions to our understanding of the synthesis, transport and catabolism of plasma lipoproteins, for showing the effects of drugs and aging on liver structure and function, for describing the mechanism of transport of peptide hormones and immunoglobulin to their sites of action and for the co-discovery of the M cell and its role in the intestinal immune response.
1986	Aaron J. Marcus, M.D.	New York	For persistent innovation in the study of platelet function, leading to the first isolation of a coagulation-promoting lipid from human platelets, for discovering arachidonic acid in platelets, for the first direct demonstration of the interaction of the acetyl group of

			aspirin with platelets and for the demonstration of platelet-leukocyte interactions.
1987	Gerald M. Reaven, M.D.	Palo Alto	For demonstration of the relationship between degree of hyperglycemia and insulin response to oral glucose, for the conceptual definition, subsequent quantification, and major development of the idea that insulin resistance is a major factor in the pathogenesis of NIDDM, for bringing understanding to the abnormal lipoprotein metabolism characteristic of diabetics, and for persistent leadership in the application of research knowledge to the treatment of diabetes.
1988	Lawrence F. Eng, Ph.D.	Palo Alto	For identification, characterization and immunocytochemical studies of glial fibrillary acidic protein (GFAP), the intermediate filament protein of differentiated astrocytes. GFAP has become a prototype antigen in central nervous tissue identification and a standard marker for fundamental and applied neurobiology at an interdisciplinary level. Antibodies to GFAP are used routinely in medical centers throughout the world to assist in the diagnosis of brain tumors.
1989	(2 awardees)		
	Edwin H. Beachey, M.D.	Memphis	For fundamental contributions to the understanding of bacterial pathogenesis, including the molecular basis for the adherence of bacteria to host cells, the molecular mechanisms of streptococcal virulence, and the immunology of Group A streptococci, particularly the immunopathogenesis of rheumatic fever and the development of novel synthetic and recombinant streptococcal vaccines.
	Makio Ogawa, M.D. PhD	Charleston	For the development of a culture system for pluripotent hematopoietic stem cells, the demonstration that differentiation of hematopoietic stem cells is a stochastic process, and the elucidation of the biological activities of hematopoietic growth factors.
1990	No award given		
1991	Young S. Kim, M.D.	San Francisco	For internationally recognized contributions in the study

			of protein digestion and absorption; the metabolism of glycoproteins and glycolipids of colon and pancreas in health and in malignancy; and the control mechanisms of patterns of colon cancer growth and differentiation.
1992	George Sachs, MB,ChB, DSc	LA Wadsworth	For internationally recognized contributions in the study of the mechanisms of gastric acid secretion and treatment of ulcer disease
1993	(2 awardees)		
	Neil Kaplowitz, M.D.	LA OPD	For the elucidation of the regulation of hepatic glutathione. Developing a comprehensive understanding of the regulation of glutathione synthesis by hormones and cysteine availability and glutathione turnover through release into bile and blood via carrier-mediated transport. Identifying a fundamental defect in mitochondrial glutathione defense in experimental alcoholic liver disease.
	John B. Hibbs, Jr., M.D.	Salt Lake City	For the discovery of the pathway and recognition of the importance of nitric acid synthesis; the demonstration of the role of nitric acid in mammalian physiology.
1994	Larry R. Squire, M.D.	San Diego	
1995	Gerald F. DiBona, M.D.	Iowa City	

(Intentionally Blank)

Appendix IIa. The Consultants on Hospitalization (White Committee), 1921-1923[1]

William Charles White, M.D., chairman, Medical director of the Tuberculosis League Hospital, Pittsburgh and former professor of neuropathology and psychiatry, Indiana University. He had been in charge of hospitalization of the tuberculous for the Red Cross in France and Italy. He was a member of the executive committee of the National Tuberculosis Association and chaired its Committee on Medical Research from 1920 until 1946.[2]

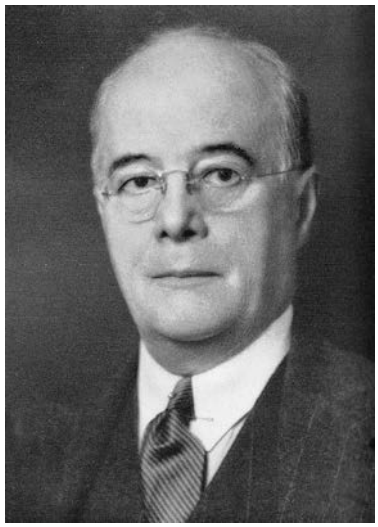


Figure AppIIa.1: William Charles White, M.D., chairman of the Committee of Consultants, 1921-1923.

Frank Billings, M.D., Dean of the faculty of Rush Medical School. Dr. Billings was later also appointed to the Medical Council but resigned before its first meeting. Billings was a leader in many fields of organized medicine. He had been president of the AMA from 1902 to 1904, then treasurer until 1911. In 1905, he led the committee responsible for starting the Council on Pharmacy and Chemistry.[3] At the time of the White Committee's activities, he was a trustee of the AMA.[4] He was an early informal advisor to the Veterans' Bureau before the Medical Council was formed.

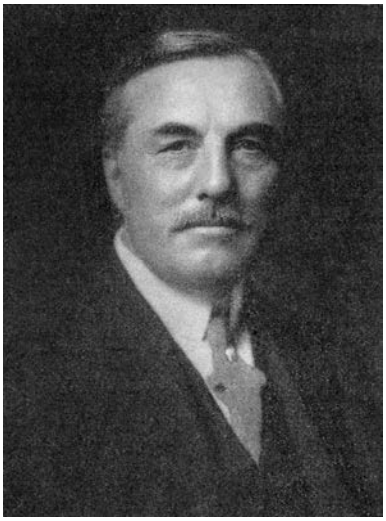


Figure AppIIa.2: Frank Billings, M.D.

John G. Bowman, an educator who was Chancellor of the University of Pittsburgh when the White Committee was active. At the time he was appointed, he had spent six years as Director of the American College of Surgeons. He had previously been secretary of the Carnegie Foundation. As Director of the American College of Surgeons, he arranged for a 1916 grant from Carnegie to launch a program of hospital standardization. He spearheaded the College's program of voluntary hospital standardization, the beginnings of the accreditation system for hospitals in the United States.[5, 6]

Pearce Bailey, M.D., Former President of the American Neurological Association. During World War I, he had established and headed a division of neurology and psychiatry in the Army. He served only three months on the White Committee, presumably resigning because of ill health, although his name appears on many of the White Committee decisions. He died in 1922.[7]

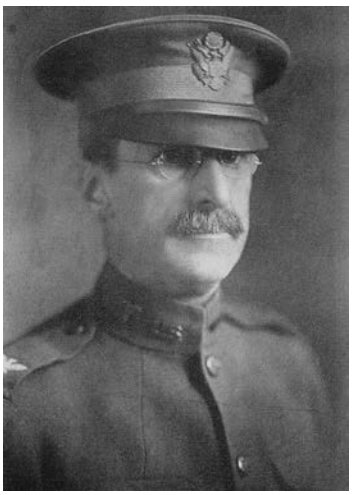


Figure AppIIa.3: Pearce Bailey, M.D.

George H. Kirby, M.D., Consultant to Director, New York Psychiatric Institute (Replaced Dr. Bailey.) Dr. Kirby was one of the original members of the Medical Council (see Appendix IIb).

Advisory committee to the White Committee:
The members of this advisory committee collected much of the information used by the White Committee in making its decisions about where new veterans' hospitals should be located. They traveled extensively, visiting potential sites for new hospitals.[8]

Thomas W. Salmon, M.D., Chairman, represented the National Committee for Mental Hygiene. Dr. Salmon was one of the original members of the Medical Council (see Appendix IIb)

Figure AppIIa.4: Thomas W. Salmon, M.D.

Haven Emerson, M.D., Medical Director the Bureau of War Risk Insurance on assignment from the Public Health Service. He had been Commissioner for Health of the City of New York before World War I, and, during WWI was Chief Epidemiologist of the A.E.F.[9] He was Medical Director of the Veterans' Bureau in 1921 (see below).

Harry A. Pattison, M.D., Supervisor of Medical Services of the National Tuberculosis Association. He was also a member of the Medical Council throughout its existence (see Table 1.2)

T. B. Kidner also represented the National Tuberculosis Association.[1]

C. H. Lavinder, M.D., Medical Director, U.S. Public Health Service. He was in charge of the Public Health Service hospitals serving the veteran. He was known for his earlier research on pellagra.[10]

Frederick C. Smith, M.D., Assistant Surgeon General and later also Medical Director, also represented the U.S. Public Health Service. Later he was an active member of the Medical Council (see Table 1.2).

Walter L. Treadway, M.D., Surgeon, U.S. Public Health Service, also represented that agency. At that time, he was associated with the Department of Preventive Medicine at Harvard Medical School. He later became an Assistant Surgeon General, as Director of the Narcotics Division, which later became the Division of Mental Hygiene of the Public Health Service.[11]

Col. C. M. Pearsall represented the National Home for Disabled Volunteer Soldiers.[1]

References

1. White, William C. and others, *Report of Consultants on Hospitalization*. 1923), 6.

2. Long, Esmond R., "Wm. Charles White." *Am Rev Tuberculosis*, 1948. **57**: 538-542.

3. Burrow, James G., *AMA: Voice of American Medicine*. (Baltimore: The Johns Hopkins Press, 1963), 74-75.

4. Anonymous obituary, "Dr. Frank Billings." *J Am Med Assn*, 1932. **99**: 1187-1188.

5. *Who Was Who in America*. Vol. 4. (Chicago: Marquis - Who's Who, Incorporated, 1968), 106.

6. Stevens, Rosemary, *In Sickness and in Wealth: American Hospitals in the Twentieth Century*. Basic Books, 1989), 116.

7. Dana, Charles L., "Obituary - Pierce Bailey, M.D." *Arch Neurol Psychiatr*, 1922. **7**: 360-364.

8. White, William C. and others, *Report of Consultants on Hospitalization*. 1923), 5-6.

9. Emerson, Haven, "Haven Emerson," in *History of the Interurban Clinical Club, 1905-1937*, Reisman, David, Editor. 1937, The John C. Winston Company: Chicago, Philadelphia and Toronto 117-118.

10. Schwarz, J.C., *Who's Who among Physicians and Surgeons*. (New York: J.C.Schwarz, 1938), 691.

11. Schwarz, J.C., *Who's Who among Physicians and Surgeons*. (New York: J.C.Schwarz, 1938), 1213-1214.

Appendix IIb. The Medical Council

The Executive Committee

Ray Lyman Wilbur, M.D.,(Figure 1.1, Chapter 1) "Permanent Chairman," was, at the time he was appointed to the Medical Council, the President of Stanford University and the President of the American Medical Association. Wilbur began his medical career in the horse and buggy days, had joined the clinical faculty of the Cooper Medical College (later Stanford Medical School) and had later been its Dean. A college friend of Herbert Hoover, in 1929 he became Hoover's Secretary of the Interior and oversaw the building of the Hoover Dam.[1] Soon after he became Secretary, he began his address to the tenth meeting of the Council with the comment that he was in a hurry. "Unfortunately, in setting this meeting for this morning, I forgot that Friday morning was the day for the meeting of the Cabinet. I realized that the deliberations of your delegation were much more important than anything which would take place at the Cabinet meeting, but I have to make a good showing and pretend that the Cabinet meeting is more significant."[2] At that meeting, Wilbur stepped down as Chairman of the Medical Council, though he stayed on as a member. Lewellys F. Barker, Emeritus Professor of Medicine at Johns Hopkins University and a founding member of the Medical Council, was elected Chairman.[3]

Lewellys F. Barker, M.D., (figure 1.8, Chapter 1) Chairman of the Medical Council after 1929, was a Canadian who had gone to Johns Hopkins Medical School for postdoctoral training and stayed on as a faculty member in pathology. From 1900 to 1905, he was Chairman of the Department of Anatomy at Rush Medical College, but then he returned to Hopkins to succeed Dr. William Osler as Chairman of Medicine. He had widespread medical interests. He had served on commissions to study tropical diseases in the Philippines and San Francisco. He was president of the National Committee for Mental Hygiene from 1909 to 1918. He was Consulting Neurologist to the Diagnostic Center at the Washington, D.C. Veterans' Hospital and had written a textbook on the nervous system. He contributed an article to the *Medical Bulletin* on epidemic encephalitis[4] and he was an editor of a journal on endocrinology. At the time the Medical Council was formed, he was no longer Chairman at Johns Hopkins, having stepped down rather than to give up his extensive private practice when the full time system for faculty was instituted there.[5] He continued to be active on the Council through its final meeting in 1939, taking part in the two conferences on medical research held in 1930 and 1935.[6-8]

H. Kennon Dunham, M.D., Vice Chairman throughout the life of the Council, was a tuberculosis expert, Associate Professor of Medicine and head of the Department of Tuberculosis at the University of Cincinnati and Medical Director of the county tuberculosis hospital. During his training, he studied anatomy, and his major early research demonstrated the x-ray findings characteristic of tuberculosis. Dr. Dunham set up the first Veterans' Bureau Diagnostic Center, established at the Cincinnati General Hospital.[9-11] He published in the *Medical Bulletin* a review of 241 cases of nontuberculous lung diseases seen at the Cincinnati Diagnostic Center in 1925 and 1926, mostly patients initially thought to have tuberculosis.[12]

Figure AppIIb.1: H. Kennon Dunham, M.D.

Malcolm T. MacEachern, M.D., the permanent Secretary of the Council, was a Canadian gynecologist who came to the United States in 1923, after having been a hospital administrator in Canada. In 1923, he became Associate Director, later Director, of hospital activities for the American College of Surgeons, a position he held until 1950. In this capacity, he coordinated the accreditation review of all Veterans' Bureau hospitals by the American College of Surgeons. He was President of the American Hospital Association (1924-5). A recognized expert in hospital organization and management, he wrote books on hospital organization and management and on medical records.[13]

Roy D. Adams, M.D., the permanent Secretary of the Executive Committee, was a Washington, D.C. internist and Professor of Clinical Medicine at George Washington University. He was the Chief Consultant for the second Diagnostic Center, established in Washington, D.C. in 1925.[14] Dr. Adams was active throughout the life of the Council. He attended the conference held in 1935 to advise the Veterans Administration about research in cardiovascular and neuropsychiatric diseases.[8]

Group on Investigation and Research

All of the members of this Group continued to be active advocates of research throughout the life of the Medical Council, except for Michael Davis, who became inactive after 1927.

Louis I. Dublin, Ph.D., Chairman, (Chapter 1, Figure 1.9) was a strong voice for establishing research in the Veterans' Bureau. A statistician who was vice-president of the Metropolitan Life Insurance Company, he had been with Metropolitan since 1909. His studies on mortality became guidelines for life insurance and public health. He spearheaded Metropolitan's programs of home nursing, health education, tuberculosis control and other welfare services for policyholders and employees. His studies of the sequelae of infectious diseases (especially typhoid fever and scarlet fever) led to an understanding of the need to control their incidence. He also studied chronic diseases, including the role of obesity.[15, 16] Dr. Dublin was an active lobbyist for improving veterans' health care as the veterans' hospitals came under increased stress toward the end of World

War II.[17] As one of the original members of the Committee on Veterans' Medical Problems,[18]he continued to advise the VA as late as 1946. Dr. Dublin's influence on the early research program is especially reflected in the statistical studies published by the chief of the Research Subsection, Dr. Matz.

Alfred E. Cohn, M.D., was another very active member of the Group on Investigation and Research. He was a cardiologist who devoted his career to clinical research. In 1909, when he returned from two years' study in Germany, he brought back with him an electrocardiograph machine, the first in the Western hemisphere. In 1911, he joined the staff of the Rockefeller Institute, bringing his electrocardiograph with him. He studied the size of the heart by x-ray, the action of cardiac drugs, the effect of aging on the heart. He classified heart diseases and compiled statistics on the various types.[19, 20] In 1924, as founding editor of the *Journal of Clinical Investigation*, he wrote a landmark editorial "Purposes in Medical Research" for the first issue.[21] He continued active on the Medical Council through its final meeting in 1939 and took take part in the 1935 conference to advise on research on cardiovascular and neuropsychiatric diseases in the Veterans Administration.[8]

Michael M. Davis, Jr., who held a Ph.D. in political science and was an expert on clinic organization, was an active early participant, both in the Group on Investigation and Research and the Group on Hospitals, Dispensaries and General Medical Welfare. Davis was an early and vigorous innovator in the economics and organization of health care in the United States. As Director of the Boston Dispensary, he examined the outcomes of clinic care, using statistical procedures. His analysis revealed that, among other problems, patients who could afford to pay something and so were not eligible for charity care but who could not afford private care were being neglected by the health care system. For workingmen with venereal diseases, he introduced evening clinics, staffed by salaried physicians instead of the volunteers who staffed the charity clinics. The salaries of these physicians were covered by a 50 cent fee from each patient. Beginning in 1925, he was one of the founders of and a leader in the Committee on the Costs of Medical Care.[22]

At the time he served on the Medical Council, Davis was Executive Secretary of the United Hospital Fund in New York.[23] In 1925, at the Veterans' Bureau's request, he conducted a study of clinic efficiency at the New York Regional Office, using an "unbiased" sample of treatment records. He found that patients' records were so scattered and cumbersome that it was virtually impossible for the treating physician to know about a patient's previous examinations and treatments.[24]

Davis attended only four meetings of the Medical Council, but he was active through the sixth meeting, in November 1926, when the Group on Investigations and Research proposed that a unified outpatient record be carried out on a trial basis.[25]

Allen K. Krause, M.D., an active member until the mid-1930s, was a specialist in tuberculosis research. During the time he was most active in Medical Council activities, he directed the Dows Laboratory at Johns Hopkins University, a privately endowed laboratory dedicated to research in tuberculosis. He was also Associate Professor of Pathology at Johns Hopkins and Editor of the *American Review of Tuberculosis.*[26, 27] In addition to his service on the research Group, he served

on the Council subcommittee to advise on the *Medical Bulletin*, and on a subcommittee to advise on outpatient care.

Figure AppIIb.2: Allen K. Krause, M.D.

Horatio M. Pollack, Ph.D., who attended all Council meetings after he was appointed at the second meeting, served as the Director of the Statistical Bureau of the New York Department of Mental Hygiene from 1911 to 1944. He was editor of *Psychiatric Quarterly* and advisor in statistics for the National Committee for Mental Hygiene.[28] He was an authority on the hospital and social aspects of mental diseases, and wrote a book on the subject.[29] He contributed an article, "Annual National Statistics of Institutions for the Insane, Feeble-Minded, Epileptic and Delinquent," to the *Medical Bulletin.*[30]

Joseph W. Schereschewsky, M.D., had been Assistant Surgeon General of the Public Health Service in charge of the division of scientific research. He conducted studies on the cause of pellagra. During his more active period on the Medical Council (1924-1929), he was on detail to Harvard University, in charge of investigations in cancer for the Public Health Service, a program that eventually led to the National Cancer Institute.[31] His epidemiological studies of the trends in cancer mortality from 1900 to 1920 showed a 56% increase, only part of which could be ascribed to factors such as improved diagnosis.[32]

Group on Neuropsychiatry

All of the members of this Group remained active in Medical Council activities except for Drs. Kirby and Salmon. Drs. White, Salmon, Barrett, Kline and Lorenz had been members, together with three other neuropsychiatrists, of a four-day conference called in 1922 and chaired by Dr. White that had resulted in an official definition of "neuropsychiatric disease" for the Veterans' Bureau's use and recommendations for the construction needs for neuropsychiatric hospitals.[33]

Daniel J. McCarthy, M.D., Chairman, was a neurologist and neuropsychologist who was professor of medical jurisprudence at the University of Pennsylvania School of Medicine. He had an

extensive record of public service and was the author of several important textbooks. A firm believer in the medical nature of psychiatric diseases, he believed that "in every case of true insanity ...there are pathological changes produced in the brain, although these may...be too subtle and recondite to be discovered by our present means of research."[34] McCarthy remained active on the Medical Council through 1929 but did not attend either of the meetings during the 1930s. He was one of the Counselors who urged the Veterans' Bureau to conduct more research. In an article in the *Medical Bulletin* referring to the epidemics of lethargic encephalitis, he wrote, "The evil effects of this one disease both mentally and physically and the chronicity of the sequellae would warrant the United States in establishing an institution of research, in connection with the Veterans' Bureau, to search out the cause and investigate the effects of the disease. One can easily estimate the cost to the Government of the Parkinsonian group alone and the sheer necessity for an intensive study of it in an institute devoted to pure research and manned by expert experts free from the necessity of hospital routine and paper work. Congress should be made to realize that the great weakness of the Veterans' Bureau is not having some such institution and that this is not due to the bureau but to the rigidity of the laws governing the bureau."[35]

Albert M. Barrett, M.D., was a strong advocate for neuropsychiatric research and attended the 1935 conference to advise on research on cardiovascular and neuropsychiatric diseases in the Veterans Administration.[8] He was chairman of the Department of Psychiatry at the University of Michigan and had established the Michigan State Psychopathic Hospital, the first university-affiliated psychiatric hospital. His interests spanned neuropathology to psychodynamics.[36]

Figure AppIIb.3: Albert M. Barrett, M.D.

C. Macfie Campbell, M.D., was Professor of Psychiatry at Harvard Medical School and medical director of the Boston Psychiatric Hospital. Primarily a clinician and teacher, he had earlier been at the Phipps Psychiatric Institute at Johns Hopkins.[37]

George H. Kirby, M.D., attended only the first and third meetings of the Medical Council, but as one of the four members of the White Committee he presumably provided "institutional memory." He was a psychiatrist and Director of the New York State Psychiatric Institute, which, during his directorship, became a part of Columbia University.[38, 39]

George M. Kline, M.D., was Commissioner for Mental Health for the State of Massachusetts. He was credited with increasing the release rate in Massachusetts mental hospitals from 8% to 48%, and for the fact that the rate of increase in mental disease in that state was below the increase in the population.[40, 41] He attended all of the meetings of the Medical Council until his death in 1933.

William F. Lorenz, M.D., a strong advocate for neuropsychiatric research, attended the 1935 conference to advise on research on cardiovascular and neuropsychiatric diseases in the Veterans Administration.[8] He was Professor of Psychiatry at the University of Wisconsin and Director of the Wisconsin State Psychiatric Institute. A veteran of the Spanish American War as well as WWI, he had participated in the U.S.P.H.S. study of pellagra. His psychiatric research included remedies for treating syphilis of the central nervous system and investigation of carbon dioxide treatment of the psychoses.[42]

Figure AppIIb.4: William F. Lorenz, M.D.

Glenn E. Myers, M.D., was a psychiatrist in practice in Los Angeles and Medical Director of the Compton Clinic. He served on the National Committee for Mental Hygiene and was a Councilor of the American Psychiatric Association.[43] He joined the Medical Council at its third meeting in 1925 and after that time attended most of its meetings. Dr. Myers contributed an article, “Personality change in the course of general medical and surgical disorders” to the *Medical Bulletin*[44] and coauthored a 1930 paper in *J.A.M.A.* with Dr. Crossman on "The Neuropsychiatric Problem in the U.S. Veterans' Bureau."[45]

Thomas W. Salmon, M.D., (Figure AppIIa.4) attended only the second and third meetings of the Medical Council, but he brought previous experience with the Veterans’ Bureau, since he had been Chairman of the Advisory Committee to the White Committee. He was a leader in the field of mental hygiene, and, at the time he joined the Medical Council, he was head of the Department of Psychiatry at Columbia University.[46, 47]

Sidney I. Schwab, M.D., a neuropsychiatrist from St. Louis and Professor of Clinical Neurology at Washington University, was active throughout the life of the Medical Council. He had served on a National Research Council committee on war neuroses.[48]

Douglas A. Thom, M.D., a psychiatrist, was Director of the Division of Mental Hygiene for the State of Massachusetts.[49] He attended all meetings of the Medical Council. He contributed two

articles to the *Medical Bulletin*, one in 1926 urging, among other recommendations, that a state-ordered psychiatric examination of accused criminals precede legal proceedings, to provide an objective assessment,[50] and one in 1930 on epilepsy.[51]

William Alanson White, M.D., another strong advocate for neuropsychiatric research, attended the 1935 conference to advise on research on cardiovascular and neuropsychiatric diseases in the Veterans Administration.[8] He had testified before the White Committee. White was the Superintendent of St. Elizabeth's Hospital in Washington, D.C., where the first American use of malarial treatment for neurosyphilis had been carried out in 1922. He was also Professor of Psychiatry at George Washington and Georgetown Medical Schools and at the US Army and US Navy Medical Schools. A strong advocate of Freudian theory, he also emphasized psychological and pathological research at St. Elizabeth's. He is credited with many advances in the care of patients with serious mental illness.[52] He wrote an article in the *Medical Bulletin* about "The therapeutic value of hospital social services."[53]

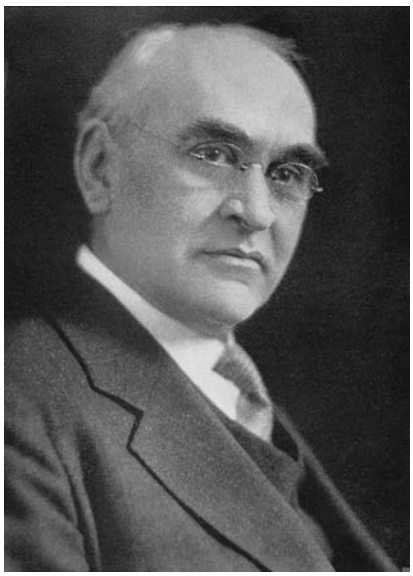


Figure AppIIb.5: William Alanson White, M.D.

Group on Tuberculosis

Drs. Baldwin, Dunn, Miller and Pattison, together with three other tuberculosis specialists, were members of a 1922 conference (chaired by Dr. Baldwin) to advise the Veterans' Bureau on tuberculosis problems.[54]

Roy D. Adams, M.D., Chairman, was also on the Executive Committee (see above).

Edward R. Baldwin, M.D., a pioneer in tuberculosis research from Trudeau Sanitorium at Saranac Lake, joined the Medical Council in 1928 and attended meetings in November 1928 and May 1929. He published widely, especially on the effects of hypersensitivity in tuberculosis, and was an early editor of *American Review of Tuberculosis.*[55] Dr. Baldwin was the president of the National Association for the Study and Prevention of Tuberculosis in 1916, when the Association, with

support from the Metropolitan Life Insurance Company (of which Louis Dublin was a key player), started a demonstration project in Framingham, Massachusetts that showed that active public health intervention would decrease incidence of tuberculosis.[56]

H.Kennon Dunham, M.D., was also on the Exexutive Committee (see above).

William LeRoy Dunn, M.D., an internist specializing in tuberculosis in Asheville North Carolina, attended the first six meetings of the Medical Council. He was well known for his therapeutic method of treating patients with complete bed rest on open porches in the fresh mountain air.[57] It seems likely that he was affiliated with the Oteen Veterans' Hospital in Asheville, the Veterans' Bureau's premier tuberculosis hospital, with 1100 beds, all for treatment of tuberculosis. Dr. Dunn was on the original ad hoc committee of the Medical Council that recommended a policy of research (see text). He spoke strongly in favor of statistical studies. At its eighth meeting, in April 1928, the Medical Council noted that he was seriously ill and voted him a "tribute".[58] He died in 1928.

Figure AppIIb.6: William LeRoy Dunn, M.D.

James Alexander Miller, M.D., Director of the Tuberculosis Service at Bellevue Hospital in New York, attended only the third meeting of the Medical Council. He had been a leader in tuberculosis control since, in 1903, he organized the Bellevue tuberculosis clinic and cared for the tuberculosis patients who were housed in tents on the hospital grounds.[59]

Figure AppIIb.7: James A. Miller, M.D.

Harry A. Pattison, M.D., specialized in the rehabilitation of patients with tuberculosis. He was Supervisor of the Medical Service of the National Tuberculosis Association and had represented that association on the Advisory Committee to the White Committee.[60] He later became Director of the Potts Memorial Institute, Livingston, New York.[61] Dr. Pattison spearheaded an effort by the Medical Council to provide transitional care for tuberculous patients who had completed their acute treatment but who needed occupational therapy and increased activity under medical supervision.[62] He also chaired a committee on Social Service and Followup.[63]

Frederick C.Smith, M.D., Assistant Surgeon General of the Public Health Service, had been one of the Public Health Service's representatives on the Advisory Committee to the White Committee.[64] He also represented the Public Health Service on the National Committee to supervise the Framingham Community Health and Tuberculosis Demonstration in 1917-1923. He testified on behalf of the Public Health Service in the 1923 Senate hearings investigating inappropriate sale of Government property, the hearings which eventually led to Charles Forbes's conviction and imprisonment. At that time, as during his service on the Medical Council, he was in charge of the Public Health Service hospital system.[65]

Group on General Medicine and Surgery

Ray Lyman Wilbur, M.D., chairman, is discussed above (Executive Committee).

Lewellys F. Barker, M.D., an internist and neurologist with widespread interests, is also discussed above (Executive Committee).

Benjamin W. Black, M.D., was appointed to the Medical Council in late 1928 and active through its 1931 meeting. He had been the Veterans' Bureau Medical Director from 1926 to 1928 and was the Medical Director of the Alameda County Hospital in California when he joined the Council.[66]

**Figure AppIIb.8: Benjamin W. Black, M.D.,
Medical Director, Veterans' Bureau, 1926-1928,
then member of the Medical Council**

George W. Crile, M.D., a well-known pioneer in surgery and Director of Research for the Cleveland Clinic,[67] attended only the first and third meetings of the Medical Council.

Joel E. Goldthwait, M.D., an orthopedic surgeon from Harvard recognized for his contributions to rehabilitation,[68] was active in the organizational stage of the Medical Council but resigned after attending the first three meetings.

Dean D. Lewis, M.D., Professor and Chairman of Surgery at Johns Hopkins School of Medicine, replaced Dr. Crile on the Medical Council. During WWI, he organized Base Hospital 13 from the staff of Presbyterian Hospital in Chicago and took it to France.[69, 70] He attended two meetings, in 1928 and 1929.

George M. Piersol, M.D., an internist with an interest in rehabilitation, was Professor of Clinical Medicine (subsequently of Physical Medicine and Rehabilitation) at the University of Pennsylvania and later Dean of its Graduate School of Medicine. He served as Medical Director for the Bell Telephone Company and editor of the *American Journal of the Medical Sciences.*[71] He attended most of the meetings of the Medical Council throughout its existence.

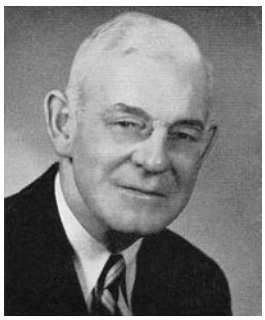


Figure AppIIb.9: George M. Piersol, M.D.

John B Walker, M.D., an orthopedic surgeon from New York City and Clinical Professor at Columbia University's College of Physicians and Surgeons, replaced Dr. Goldthwait on the Medical Council. He had been associated with veterans' health care since WWI.[72] He wrote a comprehensive review of the outcomes of all of the fractures of record sustained during the World War, published in a series of articles in the *Medical Bulletin.*[73-76] He attended all meetings of the Medical Council after 1927.

Group on hospitals, dispensaries and general medical welfare

Colonel Robert U. Patterson, M.D., (Figure 1.4) chaired this group. He was a career Army medical officer, who became Surgeon General of the Army in 1931. After his retirement from the Army in 1935, he was Dean of the medical school at the University of Oklahoma and later at the University of Maryland. Earlier, from September 1921 until February 1923, he was detailed from the Army to the Veterans' Bureau, where he served as Medical Director.[77] In that position, which he held during the notorious Forbes administration, he was said to have won "not only the respect but also the affection of his associates, because of his courage, directness, honesty and fairness." He attended meetings of the Medical Council regularly, including the 1939 meeting.

Louis H. Burlingham, M.D., also a regular attendee, was the Superintendent of Barnes Hospital and a Lecturer in hospital administration at Washington University School of Medicine.[78]

Michael M. Davis, Jr., Ph. D., was also a member of the Group on Investigations and Research (see above).

Charles A. Elliott, M.D., was appointed to the Medical Council in 1929 to replace Dr. Granger (see below). Elliott had been a member of the Yellow Fever Commission and Vice President of the American Medical Association. In 1933, he became Dean of Consultants for the Veterans' Hospital at Hines, Illinois.[79]

Sigismund S. Goldwater, M.D., Director of Mount Sinai Hospital in New York City and later Commissioner of Health for that city,[80] attended only the February, 1925 meeting.

Frank B. Granger, M.D., a neurologist and physiotherapist, was appointed to the Medical Council in 1925 and attended all of its meetings until his death in October 1928. He had organized and directed the Department of Physiotherapy, Division of Physical Rehabilitation, in the Office of the Surgeon General of the Army.[81]

Figure AppIIb.10: Frank B. Granger, M.D.

Malcolm D. MacEachern, M.D., was also a member of the Executive Committee (see above).

W. C. Rappeleye, M.D., Superintendent of New Haven Hospital and a Professor in hospital administration at Yale University School of Medicine, was also the Director of the Commission on Medical Education.[82] In 1931, he became Dean of the College of Physicians and Surgeons at Columbia University.[83] He attended most of the meetings of the Medical Council, including the final one in 1939.

Winford H. Smith, M.D., Director of The Johns Hopkins Hospital,[84] attended three meetings of the Medical Council between 1925 and 1928.

References

1. Wilbur, R.L., *The Memoirs of Ray Lyman Wilbur*. Stanford, CA: Stanford University Press, 1960.

2. Wilbur, R.L., "Address of Chairman Ray Lyman Wilbur at the Tenth Conference of the Medical Council." *US Veterans' Bureau Medical Bulletin,* 1929. **5**: 571-572.

3. "The Tenth Conference of the Medical Council." *US Veterans' Bureau Medical Bulletin,* 1929. **5**: 632-633.

4. Barker, L.F., "Clues for the Recognition of Epidemic Encephalitis in Its Different Forms and Stages, with Comments Upon Treatment." *US Veterans' Bureau Medical Bulletin,* 1929. **5**: 729-745.

5. Harvey, A.M., *Science at the Bedside: Clinical Research in American Medicine, 1905-1945*. Baltimore and London: John Hopkins University Press, 1981, 70 and 141.

6. Barker, L.F., "Lewellys Franklin Barker," in *History of the Interurban Clinical Club, 1905-1937*, Reisman, D., Editor. 1937, The John C. Winston Company: Chicago, Philadelphia and Toronto 77-78.

7. "Death of Doctor Barker, Chairman, Medical Council, Veterans' Administration." *US Veterans Administration Medical Bulletin,* 1944. **20**: 228.

8. "Report of Conference on Establishment of Research Units in Cardiovascular and Neuropsychiatric Diseases, 14 October, 1935." Washington, DC.

9. *Who Was Who in America*. Vol. 2. Chicago: A.N. Marquis Co., 1950, 165.

10. "Death of Dr. Kennon Dunham." *US Veterans Administration Medical Bulletin,* 1944. **21**: 120.

11. Anonymous obituary, "H. Kennon Dunham, 1872-1944." *Am Rev Tuberculosis,* 1944. **50**: 260-261.

12. Dunham, K. and Skavlem, J.H., "Chronic Nontuberculous Lung Infections. A Review of 700 Chest Cases." *US Veterans Bureau Medical Bulletin,* 1927. **3**: 861-866.

13. *Who Was Who in America*. Vol. 3. Chicago: Marquis - Who's Who, Incorporated, 1960, 542.

14. Schwarz, J.C., *Who's Who among Physicians and Surgeons*. New York: J.C.Schwarz, 1938, 5.

15. *Who Was Who in America*. Vol. 7. Chicago: Marquis - Who's Who, Incorporated, 1981, 165.

16. Falk, I.S., "Louis I. Dublin: November 1, 1882 - March 7, 1969." *Am J Publ Health*, 1969. **59**: 1083-1085.

17. Maisel, A.Q., "The Veteran Betrayed. How Long Will the Veterans' Administration Continue to Give Third-Rate Medical Care to First-Rate Men?" *Reader's Digest, August, 1945*, 45-50.

18. National Research Council. "Minutes of the Committee on Veterans' Medical Problems, First Meeting." *First meeting*. September 20, 1946. Washington, DC: National Academy of Sciences, 1.

19. *Who Was Who in America*. Vol. 3. Chicago: Marquis - Who's Who, Incorporated, 1960, 170.

20. Cranefield, P.F., "Alfred Einstein Cohn," in *Dictionary of American Biography*, Garraty, J.A., Editor. 1977, Charles Scribner's Sons: New York. **Supplement 6**.

21. Cohn, A.E., "Purposes in Medical Research. An Introduction to the Journal of Clinical Investigation." *J Clin Invest*, 1924. **1**: 1-11.

22. Pumphrey, R.E., "Michael M. Davis and the Development of the Health Care Movement, 1900-1928." *Societas*, 1972. **2**: 27-41.

23. *Who Was Who in America*. Vol. 5. Chicago: Marquis - Who's Who, Incorporated, 1973, 173.

24. Davis, M.M., "Improvement in Out-Patient Service, with Special Reference to Medical Records." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 108-112.

25. "News of the Medical Service. Sixth Conference of the Medical Council." *US Veterans' Bureau Medical Bulletin*, 1927. **3**: 244-245.

26. Long, E.R., "Allen Kramer Krause," in *Dictionary of American Biography*, James, E.T., Editor. 1973, Charles Scribner's Sons: New York. **Supplement 3** 431-432.

27. Willis, H.S., "Allen Kramer Krause. A Brief Biographical Story." *Am Rev Tuberculosis*, 1942. **45**: 594-606.

28. *Who Was Who in America*. Vol. 3. Chicago: Marquis - Who's Who, Incorporated, 1960, 692.

29. "'Mental Disease and Social Welfare' (Pollack)." *US Veterans Administration Medical Bulletin*, 1941. **18**: 228.

30. Pollack, H.M., "Annual National Statistics of Institutions for the Insane, Feeble-Minded, Epileptic and Delinquent." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 1037.

31. Furman, B., *A Profile of the United States Public Health Service, DHEW Publication No. (NIH) 73-369*. Washington, DC: U.S. Government Printing Office, 1973, 304 and 351.

32. "Investigation of Cancer Mortality." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 513.

33. Hines, F.T., *Annual Report of the Director of the United States Veterans' Bureau for the Fiscal Year Ended June 30, 1923*. Washington, DC: U.S. Government Printing Office, 1923, 32.

34. Powell, R.C., "Daniel Joseph McCarthy," in *Dictionary of American Biography, Supplement 6*, Beil, F.C., managing editor, Editor. 1980, Charles Scribner's Sons: New York. **Supplement 6** 402-403.

35. McCarthy, D.J., "Lethargic Encephalitis." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 895-897.

36. Waggoner, R.W., "Albert Moore Barrett," in *Dictionary of American Biography*, Schuyler, R.L., Editor. 1958, Charles Scribner's Sons: New York. **Supplement 2,** 24-25.

37. Solomon, H.C., "Charles Macfie Campbell," in *Dictionary of American Biography*, James, E.T., Editor. 1973, Charles Scribner's Sons: New York. **Supplement 3,** 127-128.

38. Brill, A.A., "George Hughes Kirby," in *Dictionary of American Biography*, Starr, H.E., Editor. 1944, Charles Scribner's Sons: New York. **Supplement 1,** 471.

39. Cheney, C.O., "George Hughes Kirby." *Mental Hygiene*, 1936. **20**: 62-65.

40. *Who Was Who in America*. Vol. 1. Chicago: A.N. Marquis Co., 1942, 684.

41. "Death of Dr. George M. Kline." *US Veterans Administration Medical Bulletin*, 1933. **9**: 429.

42. *Who Was Who in America*. Vol. 3. Chicago: Marquis - Who's Who, Incorporated, 1960, 530-531.

43. Titus, P., M.D., editor, *Directory of Medical Specialists Certified by American Boards*. New York: Columbia University Press, 1940, 928.

44. Myers, G.E., "Personality Change in the Course of General Medical and Surgical Disorders." *US Veterans' Bureau Medical Bulletin*, 1929. **5**: 925-935.

45. Crossman, E.O. and Myers, G.E., "The Neuropsychiatric Problem in the U.S. Veterans' Bureau." *J Am Med Assn*, 1930. **94**: 473-478.

46. Russell, W.L., "Thomas William Salmon," in *Dictionary of American Biography*, Malone, D., Editor. 1935, Charles Scribner's Sons: New York. **16:** 313.

47. "Thomas W. Salmon," in *History of the Interurban Clinical Club, 1905-1937*, Reisman, D., Editor. 1937, The John C. Winston Company: Chicago, Philadelphia and Toronto 256-262.

48. *Who Was Who in America*. Vol. 2. Chicago: A.N. Marquis Co., 1950, 474.

49. *Who Was Who in America*. Vol. 3. Chicago: Marquis - Who's Who, Incorporated, 1960, 848.

50. Thom, D.A., "Discussion of Dr. Hoppe's Paper on the Sources of Error in Neuropsychiatric Diagnosis." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 997-999.

51. Thom, D.A., "Epilepsy." *US Veterans' Bureau Medical Bulletin*, 1930. **6**: 435-443.

52. Overholser, W., "William Alanson White," in *Dictionary of American Biography*, Schuyler, R.L., Editor. 1958, Charles Scribner's Sons: New York. **Supplement 2** 711-712.

53. White, W.A., "The Therapeutic Value of Hospital Social Services." *US Veterans' Administration Medical Bulletin*, 1931. **7**: 774-778.

54. Hines, *Annual Report, Veterans' Bureau, Fy1923*. 33.

55. Long, E.R., "Edward Robinson Baldwin," in *Dictionary of American Biography*, Garraty, J.A. and James, E.T., Editors. 1974, Charles Scribner's Sons: New York. **Supplement 4,** 48-49.

56. Dublin, L.I., *A 40 Year Campaign against Tuberculosis*. New York: Metropolitan Life Insurance Company, 1952, 84.

57. Colby, C.D.W., "William Le Roy Dunn, M.D., 1871-1928." *Diseases of the Chest*, 1937. **3, issue 6**: 7, 24.

58. "The Eighth Conference of Medical Council." *US Veterans' Bureau Medical Bulletin*, 1928. **4**: 642-643.

59. Amberson, J.B., "James Alexander Miller," in *Dictionary of American Biography*, Garraty, J.A. and James, E.T., Editors. 1974, Charles Scribner's Sons: New York. **Supplement 4** 577-579.

60. White, W.C., Billings, F., Bowman, J.G. and Kirby, G.H., *Report of the Consultants on Hospitalization Appointed by the Secretary of the Treasury to Provide Additional Hospital Facilities under Public Act 384 (Approved March 4, 1921)*. Washington, DC: U.S.Government Printing Office, 1923, 4-6.

61. *US Veterans Administration Medical Bulletin*, 1943. **19**: 471.

62. "Minutes of the Third Medical Council Meeting, 27-28 February, 1925." 13.

63. "Program of the Ninth Conference of the Medical Council with the Director and the Medical Director of the United States Veterans' Bureau, 12-14 November, 1928." *Medical Council*. Washington, DC, 2.

64. White et al., *Report of the Consultants on Hospitalization*

65. Smith, F.C., M.D., witness. "Testimony of Doctor Frederick Charles Smith." *Hearings Before the Select Committee on Investigation of Veterans' Bureau, United States Senate*. Washington, D.C.: Government Printing Office, 651-664.

66. *Who Was Who in America*. Vol. 2. Chicago: A.N. Marquis Co., 1950, 64.

67. Earle, A.S., "George Washington Crile," in *Dictionary of American Biography*, James, E.T., Editor. 1973, Charles Scribner's Sons: New York. **Supplement 3** 200-203.

68. "Notes and Discussion." *US Veterans' Bureau Medical Bulletin*, 1926. **2**: 330.

69. Brieger, G.H., "Dean De Witt Lewis," in *Dictionary of American Biography*, James, E.T., Editor. 1973, Charles Scribner's Sons: New York. **Supplement 3** 457-458.

70. David, V.C., "Dean Dewitt Lewis, M.D.: 1874-1941." *Arch Surg*, 1941. **43**: 1150-1152.

71. *Who Was Who in America*. Vol. 4. Chicago: Marquis - Who's Who, Incorporated, 1968, 573-574.

72. *Who Was Who in America*. Vol. 2. Chicago: A.N. Marquis Co., 1950, 553.

73. Walker, J.B., "Late Results of Fractures of the Long Bones - a Statistical Study of World War Cases - I." *United States Veterans' Bureau Medical Bulletin*, 1927. **3**: 293-314.

74. Walker, J.B., "Late Results of Fractures of the Long Bones - a Statistical Study of World War Cases - II." *United States Veterans' Bureau Medical Bulletin*, 1927. **3**: 409-427.

75. Walker, J.B., "Late Results of Fractures of the Long Bones - a Statistical Study of World War Cases - III." *United States Veterans' Bureau Medical Bulletin*, 1927. **3**: 525-543.

76. Walker, J.B., "Late Results of Fractures of the Long Bones - a Statistical Study of World War Cases - IV." *United States Veterans' Bureau Medical Bulletin*, 1927. **3**: 651-657.

77. "Former Medical Director Becomes Surgeon General of the Army." *US Veterans Administration Medical Bulletin*, 1931. **7**: 783-784.

78. *Who Was Who in America*. Vol. 2. Chicago: A.N. Marquis Co., 1950, 92.

79. "Death of Dr. Charles A. Elliott." *US Veterans Administration Medical Bulletin*, 1939. **16**: 191.

80. Duffy, J., "Sigismund Schulz Goldwater," in *Dictionary of American Biography*, James, E.T., Editor. 1973, Charles Scribner's Sons: New York. **Supplement 3**.

81. *Who Was Who in America*. Vol. 1. Chicago: A.N. Marquis Co., 1942, 476.

82. *Who Was Who in America*. Vol. 7. Chicago: Marquis - Who's Who, Incorporated, 1981, 470.

83. Lamb, A.R., *The Presbyterian Hospital and the Columbia-Presbyterian Medical Center*. New York: Columbia University Press, 1955, 285-286.

84. *Who Was Who in America*. Vol. 4. Chicago: Marquis - Who's Who, Incorporated, 1968, 881.

Appendix IIc. The Committee on Veterans' Medical Problems (1946-1959)

Ad Hoc Committee on Veterans Medical Problems (1946)
(Formed to Establish the NAS-VA Collaboration)

Dr. Edward Churchill, Professor of Surgery, Harvard Med School Boston, MA, chairman
Dr. Norman Q. Brill, Veterans Administration
Dr. W. McK. Craig, Prof of Neurosurgery, Univ of Minnesota, Mayo Clin, Rochester, MN
Dr. Louis I. Dublin, Metropolitan Life Insurance Company
Dr. Perrin H. Long, Professor of Preventive Med, Johns Hopkins School of Med, Baltimore, MD
Dr. William S. McCann, Professor of Medicine, University of Rochester, Rochester, NY
Dr. Harold A. Sofield, Assistant Professor of Bone and Joint Surg, Northwestern Univ Sch of Med
Dr. Milton C. Winternitz, Prof of Pathology, Yale University School of Medicine, New Haven, CT
Dr. Harold G. Wolff, Associate Prof of Medicine, Cornell Univ Medical College, New York, NY

NAS Staff
Michael E. DeBakey, M.D., Assist Prof of Surg, Tulane Univ Sch of Medicine, New Orleans, LA; Former Director, Surgical Consultants Division, Office of The Surgeon General, U.S. Army
Beebe, Gilbert W., Ph.D. Milbank Memorial Fund; Former Chief, Analysis and Reporting Branch, Control Division, Office of The Surgeon General, U.S. Army

Committee on Veterans Medical Problems (Standing committee of the NAS)

Terms beginning 1946, 1947, or 1948
Dr. O.H. Perry Pepper, 1946-1951, chairman 1946-1950
Dr. F. J. Braceland, 1946-1948
Dr. E. D. Churchill, 1946-1948
Dr. E. McK. Craig, 1946-1949
Dr. L. I. Dublin, 1946-1948
Dr. M. E. DeBakey, 1946-1959
Dr. Perrin H. Long, 1946-1954
Dr. W. C. Menninger, 1946-1948
Dr. J. R. Miller, 1946-1948
Dr. H. J. Morgan, 1946-1948
Dr. C. P. Rhoads, 1946-1948
Dr. M. D. Winternitz, 1946-1948

Terms beginning 1949, 1950 or 1951
Dr. W. C. Davison, 1951-1959, chairman 1951-1956
Dr. H. Glenn Bell, 1951
Dr. Morris Fishbein, 1949-1951
Dr. LeRoy Johnson, 1951-1954
Dr. Chester S. Keefer, 1950-1951
Dr. Herbert H. Marks, 1949-1954
Dr. Roy Turner, 1951-1952
Dr. John C. Whitehorn, 1949-1950

Dr. Stewart Wolf, 1951-1952
Dr. Harold G. Wolff, 1949-1949
Dr. Barnes Woodhall, 1951-1952

Terms beginning 1952, 1953, or 1954
Dr. Esmond R. Long 1952-1959, chairman 1957-1958
Dr. J. E. Finesinger, 1952-1959
Dr. A. McGehee Harvey, 1952-1954
Dr. Donald Mainland, 1954-1957
Dr. H. Houston Merritt, 1952-1954

Terms beginning 1955 or later
Dr. William S. Stone, 1957-1959, chairman 1959
Dr. David A. Boyd, Jr., 1956-1957
Dr. W. Edward Chamberlain, 1957-1959
Dr. Currier McEwen, 1957-1959

Appendix IId. Central Advisory Committee on Radioisotopes (1947-1961)

(Constant membership, except for Dr. Morgan, who left the committee sometime between 1952 and 1959.)

Stafford Warren, M.D., Dean, UCLA School of Medicine, Los Angeles, CA, chairman; formerly Chief Medical Officer, Manhattan Engineer Project, 1943-46, Special consultant for Western labs

Hymer Friedell, M.D., Professor of Radiology, Western Reserve School of Medicine, formerly Deputy Chief Medical Officer, Manhattan Engineer Project, 1943-46, Special consultant for Central labs

Shields Warren, M.D., Professor of Pathology, Harvard Medical School, Boston, MA, Director, Division on Medicine and Biology, Atomic Energy Commission, 1947-1952, Special consultant for Eastern labs

Perrin H. Long, M.D., Professor of Preventive Medicine, Johns Hopkins University, Baltimore, MD

Hugh Morgan, M.D., Professor of Medicine, Vanderbilt University, Nashville, TN

(Intentionally Blank)

Appendix IIe. Advisory Committee on Research

(Constant membership, 1955-1960)

Hayman, Joseph M., Jr., M.D., Dean, Tufts College Medical School, Boston, MA
Chairman

Amberson, James Burns, M.D., Professor of Medicine, College of Physicians and Surgeons, Columbia University, later Consultant, Chest Service, Bellevue Hospital, New York, NY

Berryhill, Walter Reese, M.D., Dean, University of North Carolina School of Medicine, Chapel Hill, NC

Moyer, Carl A., M.D., Professor of Surgery, later Chairman, Department of Surgery, Washington University School of Medicine, St. Louis, MO

Wolff, Harold G., M.D., Professor of Medicine, later Professor of Neurology, Cornell University Medical College, New York, NY

(Intentionally Blank)

Appendix IIf. Advisory Committee on Research (1961-1968)*

Wolff, Harold G., M.D. 1961 Prof. Neurology, Cornell Univ. Med. College
Chairman 1961

Warren, Stafford L., M.D. 1961-1962; 1967-1968 Dean, UCLA School of Medicine
Chairman 1962

Child, Charles G., III, M.D. 1961-1968 Chairman, Department of Surgery, University of Michigan Medical School

Mirsky, I. Arthur, M.D. 1961-1964 Chairman, Department of Clinical Science, University of Pittsburgh School of Medicine

Rose, Harry M., M.D. 1961-1964 Chairman, Department of Microbiology, Columbia University College of Physicians and Surgeons

Stead, Eugene A., Jr., M.D. 1961-1968 Chairman, Department of Medicine, Duke University School of Medicine

Stellar, Eliot, Ph.D. 1961-1968 Institute of Neurological Sciences, University of Pennsylvania School of Medicine

Ebert, Richard V., M.D. 1963-1968 Professor and Head, Department of Medicine, University of Arkansas School of Medicine

Stein, Marvin, M.D., 1965-1968 Professor of Psychiatry, Cornell Medical School

Leavitt, Lewis A., M.D.1967-1968 Chairman, Department of Physical Medicine, Baylor University College of Medicine

** Source: Listings in the annual reports (Medical Research in the Veterans Administration). The committee chairman is not listed after 1962.*

(Intentionally Blank)

Appendix IIg. Research Program Committees Active in FY 1964

Basic sciences

VA members:
Henry Kamin, Ph.D., Durham, Chairman
Dexter S. Goldman, Ph.D., Madison
Leslie Zieve, M.D., Ph.D., Minneapolis
Leon Bernstein, Ph.D., San Francisco
Consultant:
Philip Handler, Ph.D., Duke University
Coordinator:
Joe Meyer, Ph.D., VACO

Cancer

VA members:
Ludwig Gross, M.D., Bronx
Julius Wolf, M.D., Bronx
Lino Arduino, M.D., Des Moines
Helmut R. Gutman, M.D., Minneapolis
Gustave Kaplan, M.D., New York
Henry P. Close, M.D., Philadelphia
George A. Higgins, M.D., Washington, DC
Raymond Yesner, M.D., West Haven
Consultants:
Sidney Farber, M.D., Harvard
Kenneth M. Endicott, M.D., Director, NCI
Warren H. Cole, M.D., University of Illinois
Sidney Weinhouse, M.D., Temple
Coordinator:
Lyndon E. Lee, M.D., VACO

Cardiovascular diseases

VA members:
Henry K. Schoch, M.D., Ann Arbor
Elvin E. Eddelman, M.D., Birmingham
Maurice B. Strauss, M.D., Boston
Craig Borden, M.D., Chicago
Mark W. Wolcott, M.D., Coral Gables
Benjamin Friedman, M.D., Dallas
E. Harvey Estes, M.D., Durham
Morton L. Pearce, M.D., Los Angeles
Milton Rubini, M.D., Los Angeles
Mervin J. Goldman, M.D., Oakland
Eli Ramirez, M.D., San Juan
Harold Dodge, M.D., Seattle

Edward Freis, M.D., Washington, DC
Consultant:
James V. Warren, M.D., Ohio State College of Medicine
Coordinator:
Harold W. Schnaper, M.D., VACO

Infectious disease
VA members:
William Merchant, M.D., Ann Arbor, Chairman
Charles Hurwitz, Ph.D., Albany
Lewis J. Griffith, Ph.D., Batavia
Thomas G. White, Ph.D., Dallas
Sydney M. Finegold, M.D., Los Angeles
Wendell H. Hall, M.D., Minneapolis
Horace H. Zinneman, M.D., Minneapolis
Lawrence G. Wayne, Ph.D., San Fernando
H. Brownell Wheeler, M.D., West Roxbury
Consultants:
L. Joe Berry, Ph.D., Bryn Mawr College
M. Michael Sigel, Ph.D., Variety Children's Research Foundation, Miami
Coordinator:
James H. Matthews, M.D., VACO

Pulmonary disease
VA members:
Roy H. Behnke, M.D., Indianapolis, Chairman
William Hentel, M.D., Albuquerque
Ralph A. Vogel, Ph.D., Atlanta
Kaye Kilbourne, M.D., Durham
Gladys L. Hobby, Ph.D., East Orange
John K. Curtis, M.D., Madison
Reeve H. Betts, M.D., Oteen
Attilio D. Renzetti, Jr., M.D., Salt Lake City
Nicholas D. D'Esopo, M.D., West Haven
Consultant:
John H. McClement, M.D., Bellevue
Coordinator:
James H. Matthews, M.D., VACO

Oral diseases
VA members:
Philip Person, D.D.S., Ph.D., Brooklyn, Chairman
Irwin W. Scopp, D.D.S., New York, secretary
Harold H. Niebel, D.D.S., Chicago WS
James B. Taylor, D.D.S., Long Beach
Joseph L. Rabinowitz, Ph.D., Philadelphia

Consultants:
Herbert K. Cooper, D.D.S., Lancaster, PA
Harry Lyons, D.D.S., Dean, School of Dentistry, Medical College of Virginia
Coordinator:
William M. Goodwin, D.D.S., VACO

Psychiatry, neurology and psychology

VA members:
Alex D. Pokorney, M.D., Houston, Chairman
Norman Geschwind, M.D., Boston
Lewis J. Sherman, Ph.D., Brockton
Robert L. Green, M.D., Durham
Kevin Barron, M.D., Hines
Janet T. Spence, Ph.D., Iowa City
Sidney Cohen, M.D., Los Angeles
Edward C. Beck, Ph.D., Salt Lake City
Lewis Bernstein, Ph.D., Wood
Consultant:
David A. Hamburg, M.D., Stanford
Coordinators:
Samuel C. Kaim, M.D., VACO
Richard N. Filer, Ph.D., VACO

(Intentionally Blank)

Appendix IIh. Program Evaluation Committees (1967-1968)

These committees initiated the systematic peer review of individual research programs within the medical research program. They are mentioned in the FY 1966 annual report to the Congress, which states that they have gradually supplanted the Research Program Committees. However, their memberships are listed only in the FY1967 and 1968 annual reports. They were succeeded in 1969 by the Research Evaluation Committees, and in 1972 by the Merit Review Boards. Except where noted, members are listed for both years.

Audiology and Speech Pathology Research

Hardy, William G., Ph.D. John Hopkins University, Baltimore, MD, Chairman
Eisenson, Jon, Ph.D. Stanford University, Palo Alto, CA
Jerger, James, Ph.D. Baylor University, Houston, TX
Knox, Albert W., Ph.D. VAH Kansas City, MO
Schuell, Hildred M., Ph.D. VAH Minneapolis, MN
Simon, George, Ph.D. VAH Washington, DC
Coordinator: Matthews, James H., M.D. Chief, Clinical Res in Pulmonary Diseases, VACO

Basic Sciences Research

van Wagtendonk, Willem J., Ph.D. VAH Coral Gables, FL, Chairman
Clark, William G., Ph.D. VAH Sepulveda, CA
Fisher, Edwin R., M.D. VAH Pittsburgh, PA
Fisher, Harvey F., Ph.D. VAH Kansas City, MO
Johnson, Shirley A., Ph.D. VAH Washington, DC
Linker, Alfred, Ph.D. VAH Salt Lake City, UT
Singer, Thomas P., Ph.D. VAH San Francisco, CA
Sinex, Marott, Ph.D. Boston University, Boston, MA
Towbin, Eugene J., M.D., Ph.D. VAH Little Rock, AK
Tyler, Albert, Ph.D. California Institute of Technology, Pasadena, CA
Utter, Merton, Ph.D. Western Reserve University, Cleveland, OH
Yuwiler, Arthur, Ph.D. VAH Los Angeles, CA
Coordinator: Meyer, Joe, Ph.D. Chief, Research in Basic Science, VACO

Cardiovascular Research

Pearce, Morton L., M.D. VAH Los Angeles, CA, Chairman
Cohn, Jay N., M.D. VAH Washington, DC
Frederickson, Donald S., M.D. (1968) National Heart Institute, Bethesda, MD
Goldman, Mervin J., M.D. VAH San Francisco, CA
Stamler, Jeremiah, M.D. (1968) City of Chicago Board of Health, Chicago, IL
Warren, James V., M.D. (1968) Ohio State University Medical School, Columbus, OH
Coordinator: Schnaper, Harold W., M.D. Codirector, Cardiovascular Research & Training Center, University of Alabama Medical Center, Birmingham, AL

Endocrinology and Metabolism

Oliner, Leo, M.D. VAH Indianapolis, IN , Chairman
Boling, Eldon A., M.D. VAH Boston, MA

Bollett, Alfred Jay, M.D. Medical College of Georgia, Augusta, GA
Frawley, Thomas F., M.D. St. Louis University School of Medicine, St. Louis, MO
Nelson, Don, M.D. Latter-day Saints Hospital, Salt Lake City, UT
Rich, Clayton, M.D. VAH Seattle, WA
Schwartz, Theodore B., M.D. Presbyterian-St. Luke's Hospital, Chicago, IL
Coordinator: Rosenberg, C.A., M.D. Assistant Director, Education Service, VACO

Hematology Research
Heller, Paul, M.D. VAH Chicago, IL (West Side), Chairman
Cartwright, George E., M.D. University of Utah College of Medicine, Salt Lake City, UT
Gurney, Clifford, M.D. Rutgers University Medical School, New Brunswick, NJ
Hall, Charles A., M.D. VAH Albany, NY
Jaffee, Ernest Richard, M.D. Albert Einstein College of Medicine, Bronx, NY
Kraus, Alfred P., M.D. University of Tennessee College of Medicine, Memphis, TN
McFarland, William, M.D. VAH Washington, DC
Scott, James L., M.D. VAH Los Angeles, CA
Sundberg, Dorothy R., M.D. University of Minnesota Medical School, Minneapolis, MN
Whitcomb, Walter H., M.D. VAH Oklahoma City, OK
Coordinator: Nadel, Eli M., M.D. Chief of Research in Pathology, Hematology and Laboratory Medicine, VACO

Infectious Disease Research
Merchant, William R., M.D. VAH Ann Arbor, MI, Chairman
Berry, L. Joe, Ph.D. Bryn Mawr College, Bryn Mawr, PA
Hobby, Gladys L., Ph.D. VAH East Orange, NJ
Lepper, Mark H., M.D. Presbyterian-St. Luke's Hospital, Chicago, IL
Sigel, M. Michael, Ph.D. The Variety Children's Research Foundation, Miami, FL
Woods, Alexander H., M.D. VAH Tucson, AZ
Coordinator: Matthews, James H., M.D. Chief, Clinical Res in Pulmonary Diseases, VACO

Oral Diseases
Shannon, Ira L., D.M.D., M.S.D VAH Houston, TX, Chairman
Giddon, Donald, D.M.D., Ph.D. Tufts University of Dental Medicine, Boston, MA
Hoerman, Cpt. Kirk C., DC, USN, D.D.S. Office of Naval Research, Washington, DC
Kapur, Krishan K., D.D.S., D.M.D., M.S. VAH Boston, MA
Person, Philip, D.D.S., Ph.D. VAH Brooklyn, NY
Phillips, Ralph W., M.S., D. Sc. Indiana University School of Dentistry, Indianapolis, IN
Coordinator: Chauncey, Howard H., Ph.D., D.M.D. Chief, Research in Oral Diseases, VACO

Pathology and Laboratory Medicine Research
Yesner, Raymond, M.D. VAH West Haven, CT, Chairman
Benson, Ellis S., M.D. University of Minnesota Medical Center, Minneapolis, MN
Bloodworth, J.M.B., M.D. VAH Madison, WI
Cote, Roger A., M.D. VAH Boston, MA
Ende, Norman, M.D. VAH Nashville, TN
Fisher, Edwin R., M.D. University of Pittsburgh, Pittsburgh, PA

Gyorkey, Ferenc, M.D. VAH Houston, TX
Kinney, Thomas D., M.D. Duke University Medical Center, Durham, NC
MacDonald, Richard A., M.D. VAH Denver, CO
Stowell, Robert E., M.D. University of California, Davis, CA
Wissler, Robert, M.D. University of Chicago, Chicago, IL
Coordinator: Nadel, Eli M., M.D. Chief, Research in Pathology, Hematology, and Laboratory Medicine, VACO

Psychiatry, Neurology, Psychology Research
Becker, Robert O., M.D. VAH Syracuse, NY, Chairman
Barron, Kevin, M.D. VAH Hines, IL
Bernstein, Lewis, Ph.D. VAH Wood, WI
Cleveland, Sidney E., Ph.D. VAH Houston, TX
Costa, Erminio, M.D. College of Physicians & Surgeons of Columbia University, NY
Hamburg, David A., M.D. Stanford University School of Medicine, Palo Alto, CA
Hamilton, Charles L., Ph.D. VAH Coatesville, PA
Mirsky, I. Arthur, M.D. University of Pittsburgh School of Medicine, Pittsburgh, PA
Oldendorf, William H., M.D. VAH Los Angeles, CA
Pierce, Chester M., M.D. VAH Oklahoma City, OK
Ross, Mathew, M.D, Harvard Medical School, Massachusetts General Hosp., Boston, MA
Stellar, Eliot, Ph.D. University of Pennsylvania, Philadelphia, PA
Zigler, Edward, Ph.D. Yale University, New Haven, CT
Coordinators:
Filer, Richard N., Ph.D. Chief, Research in Psychology, VACO
Kaim, Samuel C., M.D. Director, Staff for Alcoholism and Related Disorders, VACO

Pulmonary Disease Research
Behnke, Roy H., M.D. VAH Indianapolis, IN, Chairman
Cugell, David W., M.D. Northwestern University, Chicago, IL
Filley, Giles, M.D. University of Colorado, Denver, CO
Kilburn, Kaye H., M.D. VAH Durham, NC
Kory, Ross C., M.D. VAH Wood, WI
McClement, John H., M.D. Chest Service, Bellevue Hospital, New York, NY
Coordinator: Matthews, James H. M.D. Chief, Clinical Res in Pulmonary Diseases, VACO

Surgical Research
Webb, Watts, M.D. VAH Dallas, TX, Chairman
Campbell, Gilbert, M.D. University of Arkansas, Little Rock, AK
Cohn, Isidore, M.D. Louisiana State University, New Orleans, LA
Egdahl, Richard, M.D. University Hospital, Boston, MA
Humphrey, Edward W., M.D., Ph.D. VAH Minneapolis, MN
Pierce, Converse, M.D. Emory University, Atlanta, GA
Newton, William T., M.D. VAH St. Louis, MO
Sigel, Bernard, M.D. VAH Philadelphia, PA
Stickel, D.L., M.D.VAH Durham, NC

Vester, John, M.D., Ph.D. Good Samaritan Hospital, Cincinnati, OH
Wheeler, H. Brownell, M.D. VAH West Roxbury, MA
Coordinator: Wolcott, Mark W., M.D. Chief, Research in Surgery, VACO

Gastroenterology Research (1968 listing only)
Donaldson, Robert M., Jr., M.D. Boston University Medical School, Boston, MA, Chairman
Crane, Robert K., Ph.D. Rutgers Medical School, New Brunswick, NJ
Farrar, John T., M.D. Medical College of Virginia, Richmond, VA
Grossman, Morton I., M.D., Ph.D. VAH, Los Angeles, CA
Jackson, Francis C., M.D. VAH, Pittsburgh, PA
Menguey, Rene, M.D., Ph.D. University of Chicago School of Medicine, Chicago, IL
Summerskill, William H.J., D.M., B.Ch Mayo Clinic, Rochester, MN
Coordinator: Bernstein, Lionel M., M.D., Ph.D. Director, Research Service, VACO

Appendix IIi. Cooperative Studies Evaluation Committee

Members appointed through 1980

Lilienfeld, Abraham, M.D. 1966-1969 Professor of Chronic Diseases, School of Public Health, Johns Hopkins University, Baltimore, MD

McClaughry, Robert, M.D. 1966-1967 Chief, Eastern Research Support Center, VA Research Service, West Haven, CT

Schmidt, L.H., Ph.D. 1966-1969 Director, National Center for Primate Biology, Davis, CA

Tucker, William B., M.D. 1966-1968 Director, Medical Service, VACO, Washington, DC
Chairman, 1966-1968

Wolf, Julius, M.D. 1966-1971 Associate Chief of Staff for Research and Education, VA Hospital, Bronx, NY

Zubrod, C. Gordon 1966-1970 Scientific Director for Chemotherapy, National Cancer Institute, Bethesda, MD

Remington, Richard D., Ph.D. 1967-1971 Professor of Biostatistics, University of Michigan, Ann Arbor, MI, then Associate Dean, University of Texas School of Public Health, Houston, TX
Chairman 1969-1971

Behnke, Roy H., M.D. 1967-1971 Chief, Medical Service, VA Hospital, Indianapolis, IN

Feinstein, Alvan R., M.D. 1968-1971 Chief, Eastern Research Support Center, VA Research Service, West Haven, CT

Blaisdell, Frank William, M.D. 1969-1972 Associate Professor of Surgery, University of California, San Francisco, CA

Cole, Jonathan, M.D. 1969-1972 Superintendent, Boston State Hospital, Boston, MA

Ostfeld, Adrian, M.D. 1969-1972 Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT

Kory, Ross C., M.D. 1970-1973 Associate Chief of Staff for Research and Education, VA Hospital, Wood, WI

Schoolman, Harold M., M.D. 1970-1973 Assistant to the Director for Medical Program Development and Evaluation, National Library of Medicine, Bethesda, MD

Meinert, Curtis L., Ph.D. 1971-1974 Department of Epidemiology and Biostatistics, University of Maryland, Baltimore, MD

Chalmers, Thomas, M.D. 1972-1974 Director, Clinical Center, National Institutes for Health, Bethesda, MD
Chairman, 1972-1974

Anello, Charles, Sc.D. 1973-1975 Director, Division of Statistics, Bureau of Drugs, Food and Drug Administration, Rockville, MD

Bearman, Jacob, Ph.D. 1973-1975 Professor of Biometry, University of Minnesota, Minneapolis, MN

Jackson, Francis C., M.D. 1973-1975 Special Assistant to the Chief Medical Director for Emergency and Disaster Medical Services, VA Central Office, Washington, DC

Lipton, Morris, M.D. 1973-1975 Professor of Medicine, University of North Carolina, Chapel Hill, NC

Schwartz, Charles I., M.D. 1973-1975 Chief of Staff, VA Hospital, Lexington, KY

Zeppa, Robert, M.D. 1973-1975 Professor and Chairman, Department of Surgery, University of Miami, Miami, FL

Cornfield, Jerome 1974-1976 Professor of Biostatistics, George Washington University, Washington, DC

Finkel, Marion, M.D. 1974-1977 Deputy Director, Bureau of Drugs, Food and Drug Administration, Rockville, MD

Fries, Edward D., M.D. 1974-1977 Senior Medical Investigator, VA Hospital, Washington, DC

Littman, Armand, M.D., Ph.D. 1974-1977 Chief, Medical Service, VA Hospital, Hines, IL
Chairman, 1975-1977

Takaro, Timothy, M.D. 1975-1978 Chief of Staff, VA Medical Center, Asheville, NC

Best, William R., M.D. 1976-1979, 1983-1986; Associate Dean, University of Illinois School of Medicine, Chicago, IL
Chairman 1978-1979, Chairman, 1985-1986

Klerman, Gerald, M.D. 1976-1977, 1982-1984; Professor of Psychiatry, Harvard Medical School, Boston, MA

O'Brien, William M., M.D. 1976-1979 Professor of Medicine, University of Virginia School of Medicine, Charlottesville, VA

Brown, Byron William, Ph.D. 1977-1980 Professor and Head, Division of Biostatistics, Stanford University School of Medicine, Palo Alto, CA

Grizzle, James E., Ph.D. 1977-1980 Professor and Chairman, Department of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC

Temple, Robert, M.D. 1977-1980 Director, Division of Cardio-Renal Drug Products, Food and Drug Administration, Rockville, MD

Hollister, Leo E., M.D. 1978-1981 Chief, GRECC, VA Medical Center and Professor of Medicine and Pharmacology, Stanford University School of Medicine, Palo Alto, CA

Zimmerman, Hyman, M.D. 1978-1980 Chief, Medical Service, VAMC, and Professor of Medicine, George Washington University School of Medicine, Washington, DC
Chairman, 1980

Carr, Edward A., Jr., M.D. 1979-1982 Professor and Chairman, Department of Phamacology and Therapeutics, School of Medicine, State University of New York, Buffalo, NY

Colton, Theodore, Sc.D. 1979-1982 Professor of Public Health, Epidemiology and Biostatistics, Boston University School of Public Health, Boston, MA

Nichols, Ronald Lee, M.D. 1979-1981 Professor of Surgery, Tulane University School of Medicine, New Orleans, LA

Colwell, John A., M.D., Ph.D. 1980-1983 Associate Chief of Staff for Research and Development, VA Medical Center and Professor of Medicine, University of South Carolina School of Medicine, Charleston, SC
Chairman, 1982-1983

Davis, Clarence E., Ph.D. 1980-1983 Professor of Biostatistics, School of Public Health, University of North Carolina, Chapel Hill, NC

Knatterud, Genell L., Ph.D. 1980-1983 Vice President, Maryland Medical Research Institute, Baltimore, MD

Sobel, Solomon, M.D. 1980-1983 Director, Division of Metabolism and Endocrinology, Food and Drug Administration, Rockville, MD

(Intentionally Blank)

Appendix IIj. Career Development Committee

(called Selection Committee For Clinical Investigators before 1971)

Members appointed before 1981

Appointed before 1960

Amberson, James B., M.D. 1956-1960 Professor of Medicine, College of and Surgeons, Columbia University, New York, NY
Chairman 1956-1960

Moyer, Carl A., M.D. Professor of Surgery, Washington Univ. School of Medicine, St. Louis, MO
Chairman 1961

Finland, Maxwell, M.D. 1956-1968 Associate Professor of Medicine, Harvard Medical School, Boston, MA
Chairman 1962-1968

Dorst, Stanley E., M.D. 1956-1961 Dean, School of Medicine, Univ. of Cincinnati, Cincinnati, OH

Wolff, Harold G., M.D. 1956-1960 Professor of Medicine, Cornell University Medical College, New York, NY

Appointed 1960-1964

Eichna, Ludwig W., M.D. 1961-1964 Chairman, Department of Medicine, State University of New York, Downstate, Brooklyn, N.Y.

Stare, Fredrick J., M.D. 1961-1968 Professor and Head, Department of Nutrition, Harvard University School of Public Health, Boston, MA

Wolf, Stewart G. Jr., M.D. 1961-1968 Chairman, Department of Medicine, University Oklahoma School of Medicine, Oklahoma City, OK

Altemeier, William A., M.D. 1962-1963 Professor of Surgery, University of Cincinnati School of Medicine, Cincinnati, OH

Howell, James T., M.D. 1962-1964 Assistant Director, Henry Ford Hospital, Detroit, MI

Danowski, Thaddeus, M.D. 1964-1970 Professor of Research, University of Pittsburgh School of Medicine, Pittsburgh, PA

Rhoads, Jonathan, M.D. 1964-1970 The I. S. Ravdin Institute, University of Pennsylvania Hospital, Philadelphia, PA

Volker, Joseph F., M.D. 1964-1972 Director of Research and Graduate Studies, Medical School of Alabama, 1919 Seventh Avenue, South, Birmingham, AL

Appointed 1965-1969

Sherry, Sol, M.D. 1967-1971 Professor of Medicine, Washington University School of Medicine, St. Louis, MO
Chairman 1969-1971

Goldberg, Leon I., M.D., Ph. D. 1969-1973 Director, Division of Clinical Pharmacology, Emory University School of Medicine, Atlanta, GA

Silen, William, M.D. 1969-1973 Chairman, Department of Surgery, Beth Israel Hospital, Harvard Medical School, Boston, MA

Siperstein, Marvin, M.D., Ph.D. 1969-1973 Professor of Medicine, University of Texas Medical School at Dallas, Dallas, TX

Appointed 1970-1974

Robins, Eli, M.D. 1971-1975 Professor and Head, Department of Psychiatry, Washington University Medical School, St. Louis, MO
Chairman 1972-1975

Hook, Edward W., M.D. 1974-1978 Professor and Chairman, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA
Chairman 1976-1978

Appel, Stanley H., M.D. 1971-1975 Chairman, Division of Neurology, Duke University Medical Center, Durham, NC

Dixon, Frank J., M.D. 1971-1973 Head, Division of Experimental Pathology, Scripps Clinic and Research Foundation, La Jolla, CA

Goldstein, Leonard D., Ph. D. 1971-1976 Chairman, Department of Psychology, University of Cincinnati, Cincinnati, OH

Liddle, Grant W., M.D. 1971-1974 Chairman, Endocrinology and Metabolism Division, Vanderbilt University School of Medicine, Nashville, TN

Zuidema, George D., M.D. 1971-1974 Chairman, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

Eliel, Leonard P., M.D. 1973-1977 Vice President, University of Oklahoma Medical School, Oklahoma City, OK

McManus, J. F. A., M.D. 1973-1977 Dean, College of Medicine, Medical University of South Carolina, Charleston, SC

Salley, John J., D.D.S., Ph. D. 1973-1977 Dean, University of Maryland School of Dentistry, Baltimore, MD

Wang, Yang, M.D. 1973-1976 Associate Professor of Medicine, University of Minnesota, Minneapolis, MN

King, Thomas C., M.D. 1974-1978 Professor of Surgery, Columbia Presbyterian Medical Center, New York, NY

Pool, Judith G., Ph.D. 1974-1975 Professor of Medicine, Stanford University School of Medicine, Stanford, CA

Appointed 1975-1980

Schilling, Robert F., M.D. 1976-1980 Professor of Medicine, Univ. of Wisconsin, Madison, WI
Chairman 1978-1979

Behnke, Roy H., M.D. 1979-1982 Chairman & Professor, Department of Internal Medicine, University of South Florida College of Medicine, Tampa, FL
Chairman 1980-1982

Bergofsky, Edward H., M.D. 1975-1979 Professor, State University of New York, Stonybrook, NY

Tyor, Malcolm P., M.D. 1975-1979 Professor and Chief, Division of Gastroenterology, Duke University Medical Center, Durham, NC

Wagner, Henry N. Jr., M.D. 1975-1979 Professor of Medicine, Radiology and Environmental Health, The Johns Hopkins Medical Institution, Baltimore, MD

Freinkel, Norbert, M.D. 1975 Professor of Medicine, Northwestern University Medical School, Chicago, IL

Diamond, Ivan, M.D., Ph.D. 1976-1979 Associate Professor of Neurology, University of California School of Medicine, San Francisco, CA

Lipton, Morris, M.D., Ph.D. 1976-1979 Director, Biological Science Research Center, University of North Carolina School of Medicine, Chapel Hill, NC

Kuida, Hiroshi, M.D. 1976-1980 Professor and Chairman, Division of Cardiology, University of Utah College of Medicine, Salt Lake City, UT

Sterman, Maurice B., Ph.D. 1976-1980 Chief, Neuropsychology Research, VA Hospital, Sepulveda, CA

Bernard, Louis J., M.D. 1977-1980 Professor and Chairman, Department of Surgery, Meharry Medical College, Nashville, TN
Fullmer, Harold, D.D.S. 1977-1981 Director & Associate Dean, University of Alabama School of Dentistry, Birmingham, AL

Kowal, Jerome, M.D. 1977-1980 Chief of Staff, VA Hospital, Cleveland, Ohio

Warner, Nancy E., M.D. 1977-1978 Professor and Chairman, Department of Pathology, University of Southern California School of Medicine, Los Angeles, CA

Cluff, Leighton E., M.D. 1978-1979 Vice President, Robert Wood Johnson Foundation, Princeton, New Jersey

McCabe, William R., M.D. 1979-1983 Professor of Medicine & Microbiology, Boston University School of Medicine, Boston, MA

Suzuki, Kinuko, M.D. 1979-1982 Professor of Pathology, Albert Einstein College of Medicine, Bronx, NY

Volwiler, Wade, M.D. 1979-1983 Professor of Medicine, University of Washington School of Med., Seattle, WA

Moore, Robert Y., M.D., Ph.D. 1980-1983 Professor & Chairman, Department of Neurology, State University of New York at Stony Brook, Stony Brook, NY

Papper, Solomon, M.D. 1980-1982 Distinguished Professor and Head, Department of Medicine, University of Oklahoma Health Science Center, Oklahoma City, OK

Appendix IIk. Institutional Research Programs Evaluation Committees (Part 2)

Membership of these committees is listed here as recorded in the annual report to the Congress, Fiscal Years 1969, 1970 and 1971. The program began in Calendar Year 1968 and terminated in March, 1970. Membership was stable except where noted.

Committee A

Sprague, Charles C., M.D. Dean, University of Texas, Southwestern Medical School at Dallas, TX
Chairman 1970-1971

Wiggers, Harold C., Ph.D. Executive Vice President and Dean, Albany Medical College of Union University, Albany, NY
Chairman 1969

Aspis, Samuel L., M.D. Hospital Director, VAH, Cleveland, OH

Burch, Neil, R., M.D. Professor of Mental Science, the University of Texas Graduate School of Biomedical Sciences; Associate Professor, Psychiatry, Baylor College of Medicine; Head, Division of Psychophysiology, Texas Research Institute of Mental Sciences, Houston, TX

Howell, David S., M.D. (1969) Chief, Rheumatology and Arthritis Section, University of Miami School of Medicine, Miami, FL

Lester, Richard, M.D. Chairman, Department of Radiology, Duke University School of Medicine, Durham, NC

Nadel, Eli M., M.D. (1969) Associate Dean and Professor of Pathology, St. Louis University School of Medicine, St. Louis, MO

Rich, Clayton, M.D. (1969-1970) Associate Dean for Research and Facilities, University of Washington, Seattle, WA

Robbins, Stanley L, M.D. Professor and Chairman, Department of Pathology, Boston University School of Medicine, Boston, MA

Sigel, Bernard, M.D. (1969) Professor of Surgery and Dean, Women's Medical College of Pennsylvania, Philadephia, PA

Simeone, Fiorindo A., M.D. (1970-1971) Professor of Medical Science, Chairman, Section of Surgery, Division of Biological and Medical Sciences, Brown University, Providence, RI

Vickerstaff, Hugh Hospital Director (1970-1971), VAH, Nashville, TN

Warren, James V., M.D. Chairman, Department of Medicine, Ohio State University Medical School, Columbus, OH

Zieve, Leslie, M.D. (1970-1971) ACOS/R&E, VAH, Minneapolis, MN

Executive secretary
Libman, Gerald Chief, Office of Scientific Evaluation, VA Central Office, Washington, DC

Committee B

Burrows, Leslie R., D.D.S., Ph.D. Dean, Scholl of Dentistry, University of Colorado Medical Center, Denver, CO
Chairman 1969

Bird, Robert M., M.D. Dean, University of Oklahoma School of Medicine, Oklahoma City, OK
Chairman 1970-1971

Best, William R., M.D. Director, Midwest Research Support Center, VAH, Hines, IL

Brunson, Joel G., M.D. (1969) Chairman, Department of Pathology, University of Mississippi Medical Center, Jackson, MS

Cohn, David V., Ph.D. ACOS/R&E, VAH, Kansas City, MO

Goodale, Fairfield, Jr., M.D. (1970-1971) Chairman, Department of Pathology, the Medical College of Virginia, Virginia Commonwealth University, Richmond, VA

Gottlieb, Abraham, M., M.D. Director, VAH, Palo Alto, CA

Lhamon, William T., M.D. Professor and chairman, Department of Psychiatry, Cornell University Medical Center, New York, NY

Page, Lot B., M.D. Chief of Medicine, Newton-Wellesley Hospital, Newton Lower Falls, MA

Proctor, Donald F., M.D. Professor of Environmental Medicine, Associate Professor of Laryngology and Otology, Johns Hopkins School of Hygiene, Baltimore, MD

Ravitch, Mark, M.D. (1969) Professor of Surgery, University of Pittsburgh School of Medicine, Montefiore Hospital, Pittsburgh, PA

Waddell, William R., M.D. (1970-1971) Chairman, Department of Surgery, University of Colorado Medical Center, Denver, CO

Williams, Clyde, M.D. Chairman, Department of Radiology, University of Florida Health Center, Gainesville, FL

Executive secretary
Libman, Gerald Chief, Office of Scientific Evaluation, VA Central Office, Washington, DC

Appendix III. Merit Review Board Members Appointed 1972-1980

Merit Review Board for Alcoholism and Drug Dependence
(Clinical Pharmacology)

Cochin, Joseph, M.D., Ph.D. Professor of Pharmacology, Boston University School of Medicine, Boston, MA
Chairman, 1972-1974

Harris, Louis S., Ph.D. 1975 – 1978 Professor & Chairman, Department of Pharmacology, Medical College of Virginia, Richmond, VA
Chairman, 1975-1978

Inturrisi, Charles E., Ph.D. 1977 – 1980 Associate Professor of Pharmacology, Cornell Medical College, New York, NY
Chairman 1979-1980

Chafetz, Morris, M.D. 1972 Director, National Institute of Alcohol Abuse and Alcoholism, Rockville, MD

Cole, Jonathan O., Ph.D. 1972 – 1975 Superintendent, Boston State Hospital, Boston, MA

Davis, Virginia E., Ph.D. 1972 – 1975 Director, Neurochemistry & Addiction Research, VA Hospital, Houston, TX

Holliday, Audrey R., Ph.D. 1972 Department of Psychiatry, University of Chicago Pritzker School of Medicine, Chicago, IL

Hollister, Leo E., M.D. 1972 – 1975 Medical Investigator, VA Hospital, Palo Alto, CA

Lieber, Charles, M.D. 1972 – 1975 Chief, Section of Liver Disease and Nutrition, VA Hospital, Bronx, NY

Ludwig, Arnold M., M.D. 1972 – 1975 Professor of Psychiatry, University of Kentucky, Lexington, KY

Martin, William R., M.D. 1972 – 1973 Chief, National Institute of Mental Health Addiction Research Center, Lexington, KY

McGlothlin, William H., Ph.D. 1972-1975 Professor of Psychology, University of California, Los Angeles, CA

Mclsaac, William M., M.D. 1972 – 1973 Director, Texas Research Institute of Mental Sciences, Houston, TX

Nowlis, Vincent, Ph.D. 1972 – 1975 Consultant, Drug Abuse Council, Washington, DC

Way, Edward L., Ph.D. 1972 – 1975 Professor of Pharmacology and Experimental Therapeutics, University of California Medical Center, San Francisco, CA

Jarvik, Lissy, M.D. 1974 – 1977 Chief, Psychogenetics Unit, VA Hospital (Brentwood), Los Angeles, CA

Kissin, Benjamin, M.D. 1974 – 1977 Director, Kings County Addictive Disease Hospital, Brooklyn, NY

Mayfield, Demmie G., M.D. 1974 – 1977 Chief of Psychiatry, VA Hospital, Providence, RI

Meyer, Roger E., M.D. 1978 – 1981 Chairman, Department of Psychiatry University of Connecticut School of Medicine, Farmington, CT
Chairman, 1980-1981

Mandel, H. George, Ph.D. 1975 – 1978 Professor and Chairman, Department of Pharmacology, George Washington University School of Medicine, Washington, DC

Schildkraut, Joseph J., M.D. 1975 – 1978 Professor of Psychiatry, Massachusetts Mental Health Center, Boston, MA

McMillan, Donald E., Ph.D. 1976 – 1979 Professor of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, NC

McNay, John L. Jr., M.D. 1976 – 1979 Department of Medicine, VA Hospital, San Antonio, TX

Robinson, Donald S., M.D. 1976 – 1979 Associate Professor of Medicine, University of Vermont College of Medicine, Burlington, VT, later Professor & Chairman, Department of Pharmacology, Marshall University School of Medicine, Huntington, WV

Mendelson, Jack H., M.D. 1977 – 1980 Professor of Psychiatry, Director, Alcohol and Drug Abuse Research Center, McLean Hospital, Belmont, MA

Rennick, Barbara R., M.D. 1977 – 1980 Professor of Pharmacology, State University of New York at Buffalo, Buffalo, NY

Martin, William R., M.D., 1978 – 1981 Professor and Chairman, Department of Pharmacology, University of Kentucky, Lexington, KY

Nuite-Belleville, Jo Ann, Ph.D. 1978 - 1981 Assistant Professor of Pharmacology, Georgetown University School of Medicine, Washington, DC

Nies, Alexander, M.D. 1979 – 1982 Professor of Psychiatry, Marshall University School of Medicine, Huntington, WV, later Psychiatry Service, VA Medical Center, Newington, CT

Perrier, Donald, Ph.D. 1979 – 1982 Associate Professor of Pharmaceutical Sciences, College of Pharmacy, University of Arizona, Tucson, AZ

Woods, James H., Ph.D. 1979 – 1982 Associate Professor of Pharmacology and Psychology, University of Michigan School of Medicine, Ann Arbor, MI

Blake, David A., Ph.D. 1980 – 1983 Associate Professor of Pharmacology, Johns Hopkins School of Medicine, Baltimore, MD

Finkle, Bryan S., Ph.D. 1980 – 1983 Associate Professor of Biochemistry, Phamacology & Toxicology, University of Utah, Salt Lake City, UT

O'Brien, Charles P., M.D. 1980 – 1983 Director, Drug Dependency Treatment and Research Unit, VA Medical Center, Philadephia, PA

Merit Review Board for Basic Sciences

Estabrook, Ronald W., Ph.D. 1972-1975 Professor of Biochemistry, later Dean, Graduate School of Medical Sciences, University of Texas, Dallas, TX
Chairman, 1972-1975

Barker, Robert, Ph.D. 1975-1978 Professor & Chairman, Department of Biochemistry, Michigan State University, East Lansing, MI
Chairman, 1976-1978

Orme-Johnson, William H., III, Ph.D. 1977-1980 Professor of Biochemistry, University of Wisconsin School of Medicine, Madison, WI
Chairman, 1978-1980

Blakley, Raymond L., Ph.D., D. Sc. 1978-1980 Professor of Biochemistry, University of Iowa College of Medicine, Iowa City, IA
Chairman 1980-1981

Fishman, William H., Ph.D. 1972-1975 Director, Cancer Research Center, Tufts University School of Medicine Boston, MA

Kamin, Henry, Ph.D. 1972-1975 Professor of Biochemistry, Duke University Medical Center, Durham, NC

Lindsay, Raymond H., Ph.D. 1972-1975 Director of Pharmacology Research, VA Hospital, Birmingham, AL

Linker, Alfred, Ph.D. 1972-1975 Research Biochemist, VA Hospital, Salt Lake City UT

Moldave, Kivie, Ph.D. 1972-1975 Professor of Biochemistry, California College of Medicine, University of California, Irvine, CA

Porter, John W., Ph.D. 1972-1975 Chief, Lipid Metabolism Laboratory, Madison, WI

Putnam, Frank, Ph.D. 1972-1975 Professor of Molecular Biology and Biochemistry, Indiana University, Bloomington, IN

Setlow, Jane K., Ph.D. 1972-1975 Biology Division, Oak Ridge National Laboratory, Oak Ridge, TN

Srere, Paul, Ph.D. 1972-1975 Chief, Biochemistry Unit, VA Hospital, Dallas, TX

Wold, Finn, Ph.D. 1972-1975 Professor, later also Head, Department of Biochemistry, University of Minnesota Medical School, Minneapolis, MN

Irving, Charles C., Ph.D. 1974-1977 Chief, Cancer Research Laboratory, VA Hospital, Memphis, TN

Vahouny, George V., Ph.D. 1974-1977 Professor of Biochemistry, George Washington University School of Medicine, Washington, DC

Williams, Charles H., Jr., Ph.D. 1974-1977 Research Biochemist, VA Hospital, Ann Arbor, MI

Jones, Mary Ellen, Ph.D. 1975-1978 Professor of Biochemistry, University of Southern California School of Medicine, Los Angeles, CA

Vesell, Elliot S., M.D. 1975-1978 Professor and Chairman, Department of Pharmacology, Pennsylvania State University College of Medicine, Hershey, PA

Willis, John S., Ph.D., 1975-1978 Professor of Physiology and Biophysics University of Illinois, Urbana, IL

Atkinson, Daniel, Ph.D. 1976-1979 Professor of Chemistry, University of California, Los Angeles, CA

Bitensky, Mark, M.D. 1976-1979 Professor of Pathology, Yale University School of Medicine, New Haven, CT

Fitch, Frank W., M.D., Ph.D. 1976-1979 Professor of Pathology, University of Chicago Medical School, Chicago, IL

Goldberg, Burton D., M.D. 1976-1979 Professor of Pathology, New York University School of Medicine, New York, NY

Silbert, Jeremiah E., M.D. 1976-1979 VA Outpatient Clinic, Boston, MA

Simpson, Melvin V., Ph.D. 1976-1979 Professor of Biochemistry, State University of New York School of Medicine, Stony Brook, NY

Smuckler, Edward A., M.D., Ph.D. 1976-1979 Professor & Chairman, Department of Pathology, University of California School of Medicine, San Francisco, CA

Bresnick, Edward, Ph.D. 1977-1980 Professor & Chairman, Department of Biochemistry, University of Vermont School of Medicine, Burlington, VT

Dempsey, Mary E., Ph.D. 1977-1980 Professor of Biochemistry, University of Minnesota School of Medicine, Minneapolis, MN

Farber, John L., M.D. 1978-1981 Associate Professor of Pathology, Temple University Medical School, Philadelphia, PA

Forte, Leonard R., Ph.D. 1978-1981 Research Pharmacologist, VA Hospital, and Associate Professor of Pharmacology, University of Missouri Medical School, Columbia, MO

Hoffee, Patricia A., Ph.D., 1978-1981 Professor of Microbiology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Jackson, Michael J., Ph.D. 1978-1981 Professor of Physiology, George Washington University Medical School, Washington, DC

Brown, Barbara I., Ph.D. 1979-1982 Professor of Biological Chemistry, Washington University School of Medicine, St. Louis, MO

Davidson, Eugene A., Ph.D. 1979-1982 Professor and Chairman, Department of Biochemistry, Pennsylvania State University School of Medicine, Hershey, PA

Lane, Bernard P., M.D. 1979-1982 Professor of Pathology, State University of New York Medical School, Stony Brook, NY

Noller, Harry F., Jr., Ph.D. 1979-1982 Professor of Biology, University of California, Santa Cruz, CA

Papermaster, David S., M.D. 1979-1982 Associate Professor of Pathology, Yale University Medical School, New Haven, CT

Schwartz, Stephen M., M.D. 1979-1982 Associate Professor of Pathology, University of Washington School of Medicine, Seattle, WA

Baker, Nome., Ph.D. 1980-1983 Research Biochemist, VA Medical Center (Wadsworth), Los Angeles, CA

Bodley, James W., Ph.D. 1980-1983 Professor of Biochemistry, University of Minnesota School of Medicine, Minneapolis, MN

Elbein, Alan D., Ph.D. 1980-1983 Professor of Biochemistry, University of Texas School of Medicine, San Antonio, TX

Kearney, Edna B., Ph.D. 1980-1983 Associate Research Biochemist, VA Medical Center, San Francisco, CA

Merit Review Board for Mental Health and Behavioral Sciences

Pokorny, Alex D., M.D. 1972-1975 Chief, Psychiatry and Neurology Service, VA Hospital, and Vice Chairman, Department of Psychiatry, Baylor College of Medicine, Houston, TX
Chairman, 1972-1975

Silverman, Albert, M.D. 1975-1978 Professor & Chairman of Psychiatry, University of Michigan Medical School, Ann Arbor, MI
Chairman, 1975-1978

Parsons, Oscar A., Ph.D. 1977-1980 Professor of Psychiatry & Behavioral Sciences, University of Oklahoma Medical School, Oklahoma City, OK
Chairman, 1979-1980

Cole, Jonathan O., M.D. 1979-1982 Professor of Psychiatry, Harvard Medical School, Boston, MA
Chairman, 1981-1982

Bernstein, Lewis, Ph.D. 1972-1975 Chief, Psychology Service, VA Center, Wood, WI

Freedman, Daniel X., M.D. 1972-1975 Professor of Biological Sciences and Chairman, Department of Psychiatry, University of Chicago, Chicago, IL

Hollender, Marc H., M.D. 1972-1975 Professor of Psychiatry, Vanderbilt School of Medicine, Nashville, TN

Morris, Robert, Ph.D. 1972-1975 Professor of Social Planning, Director, Levinson Gerontological Policy Institute, Brandeis University, Waltham, MA

Nathan, Peter E., Ph.D. 1972-1975 Professor of Psychology and Psychiatry, Rutgers University, New Brunswick, NJ

Nurnberger, John E., M.D. 1972 –1973 Professor and Chairman, Dept. of Psychiatry, Indiana University Medical School, Indianapolis, IN

Overall, John E., Ph.D. 1972-1975 Research Professor of Neurology and Psychiatry, University of Texas Medical Branch, Galveston, TX

Pishkin, Vladimir, Ph.D. 1972-1975 Chief Research Psychologist, VA Hospital, Oklahoma City, OK

Stein, Marvin, M.D. 1972-1975 Professor of Psychiatry, Mt. Sinai School of Medicine, New York, NY

Winokur, George, M.D. 1972-1975 Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

Butters, Nelson M., Ph.D. 1974-1977 Associate Chief, Psychology Research, VA Hospital, Boston, MA

Greenblatt, Milton, M.D. 1974-1977 Chief, Psychiatry Service, VA Hospital, Sepulveda, CA, Professor of Psychiatry, University of California School of Medicine, Los Angeles, CA

Hersen, Michel, Ph.D. 1974-1977 Professor of Clinical Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, PA

Beck, Edward C., Ph.D. 1975-1978 Director, Neuropsychological Research, VA Hospital, Salt Lake City, UT

Waziri, Rafiq, M.D. 1975-1978 Associate Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

Moos, Rudolf H., Ph.D. 1976-1978 Chief of Research (Psychiatry), VA Medical Center and Professor of Psychiatry, Stanford University School of Medicine, Palo Alto, CA

McKinney, William T. Jr., M.D. 1976-1979 Professor and Chairman, Department of Psychiatry, University of Wisconsin Medical School, Madison, WI

Obrist, Paul A., Ph.D. 1976-1979 Division of Health Affairs, Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC

Satz, Paul, Ph.D. 1976-1979 Professor of Psychology, University of Florida School of Medicine, Gainesville, FL

Stunkard, Albert, M.D. 1976-1979 Professor of Psychiatry, University of Pennyslvania School of Medicine, Philadelphia, PA

Fink, Max, M.D. 1977-1980 Professor of Psychiatry, State University of New York School of Medicine, Stony Brook, NY

Goldstein, Gerald, Ph.D. 1977-1980 Chief, Research Service, VA Hospital (Highland Drive), Pittsburgh, PA

Ackerman, Sigurd, M.D. 1978-1981 Assistant Professor of Psychiatry, Albert Einstein School of Medicine, Bronx, NY

Alexander, A. Barney, Ph.D. 1978-1981 Head, Dept. of Psychophysiology, National Asthma Center, Denver, CO

Andreasen, Nancy, M.D., Ph.D. 1978-1981 Associate Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

Cicchetti, Domenic V., Ph.D. 1978-1981 VA Medical Center, West Haven, CT

Fann, William E., M.D. 1978-1983 Chief, Psychiatry Service, VA Medical Center, Houston, TX

Meier, Manfred, Ph.D. 1979-1982 Professor & Director of Neuropsychology Lab, University of Minnesota School of Medicine, Minneapolis, MN

Rush, John, M.D. 1979-1982 Associate Professor, University of Texas, Southwestern Medical School, Dallas, TX

Winokur, Andy, M.D. 1979-1982 Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA

Gentry, W. Doyle, Ph.D. 1980-1983 Professor of Psychiatry & Behavioral Science, University of Texas Medical Branch, Galveston, TX

Kramer, Milton, M.D. 1980-1983 Assistant Chief, Psychiatry Service, VA Medical Center, Cincinnati, OH

Maxim, Peter E., M.D., Ph.D. 1980-1983 Associate Professor of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA

Merit Review Board for Mental Health and Behavioral Sciences

Pokorny, Alex D., M.D. 1972-1975 Chief, Psychiatry and Neurology Service, VA Hospital, and Vice Chairman, Department of Psychiatry, Baylor College of Medicine, Houston, TX
Chairman, 1972-1975

Silverman, Albert, M.D. 1975-1978 Professor & Chairman of Psychiatry, University of Michigan Medical School, Ann Arbor, MI
Chairman, 1975-1978

Parsons, Oscar A., Ph.D. 1977-1980 Professor of Psychiatry & Behavioral Sciences, University of Oklahoma Medical School, Oklahoma City, OK
Chairman, 1979-1980

Cole, Jonathan O., M.D. 1979-1982 Professor of Psychiatry, Harvard Medical School, Boston, MA
Chairman, 1981-1982

Bernstein, Lewis, Ph.D. 1972-1975 Chief, Psychology Service, VA Center, Wood, WI

Freedman, Daniel X., M.D. 1972-1975 Professor of Biological Sciences and Chairman, Department of Psychiatry, University of Chicago, Chicago, IL

Hollender, Marc H., M.D. 1972-1975 Professor of Psychiatry, Vanderbilt School of Medicine, Nashville, TN

Morris, Robert, Ph.D. 1972-1975 Professor of Social Planning, Director, Levinson Gerontological Policy Institute, Brandeis University, Waltham, MA

Nathan, Peter E., Ph.D. 1972-1975 Professor of Psychology and Psychiatry, Rutgers University, New Brunswick, NJ

Nurnberger, John E., M.D. 1972 –1973 Professor and Chairman, Dept. of Psychiatry, Indiana University Medical School, Indianapolis, IN

Overall, John E., Ph.D. 1972-1975 Research Professor of Neurology and Psychiatry, University of Texas Medical Branch, Galveston, TX

Pishkin, Vladimir, Ph.D. 1972-1975 Chief Research Psychologist, VA Hospital, Oklahoma City, OK

Stein, Marvin, M.D., 1972-1975 Professor of Psychiatry, Mt. Sinai School of Medicine, New York, NY

Winokur, George, M.D. 1972-1975 Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

Butters, Nelson M., Ph.D. 1974-1977 Associate Chief, Psychology Research, VA Hospital, Boston, MA

Greenblatt, Milton, M.D. 1974-1977 Chief, Psychiatry Service, VA Hospital, Sepulveda, CA, Professor of Psychiatry, University of California School of Medicine, Los Angeles, CA

Hersen, Michel, Ph.D., 1974-1977 Professor of Clinical Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, PA

Beck, Edward C., Ph.D. 1975-1978 Director, Neuropsychological Research, VA Hospital, Salt Lake City, UT

Waziri, Rafiq, M.D. 1975-1978 Associate Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

Moos, Rudolf H., Ph.D. 1976-1978 Chief of Research (Psychiatry), VA Medical Center and Professor of Psychiatry, Stanford University School of Medicine, Palo Alto, CA

McKinney, William T. Jr., M.D. 1976-1979 Professor and Chairman, Department of Psychiatry, University of Wisconsin Medical School, Madison, WI

Obrist, Paul A., Ph.D. 1976-1979 Division of Health Affairs, Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC

Satz, Paul, Ph.D. 1976-1979 Professor of Psychology, University of Florida School of Medicine, Gainesville, FL

Stunkard, Albert, M.D. 1976-1979 Professor of Psychiatry, University of Pennyslvania School of Medicine, Philadelphia, PA

Fink, Max, M.D. 1977-1980 Professor of Psychiatry, State University of New York School of Medicine, Stony Brook, NY

Goldstein, Gerald, Ph.D. 1977-1980 Chief, Research Service, VA Hospital (Highland Drive), Pittsburgh, PA

Ackerman, Sigurd, M.D. 1978-1981 Assistant Professor of Psychiatry, Albert Einstein School of Medicine, Bronx, NY

Alexander, A. Barney, Ph.D. 1978-1981 Head, Dept. of Psychophysiology, National Asthma Center, Denver, CO

Andreasen, Nancy, M.D., Ph.D. 1978-1981 Associate Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

Cicchetti, Domenic V., Ph.D. 1978-1981 VA Medical Center, West Haven, CT

Fann, William E., M.D. 1978-1983 Chief, Psychiatry Service, VA Medical Center, Houston, TX

Meier, Manfred, Ph.D. 1979-1982 Professor & Director of Neuropsychology Lab, University of Minnesota School of Medicine, Minneapolis, MN

Rush, John, M.D. 1979-1982 Associate Professor, University of Texas, Southwestern Medical School, Dallas, TX

Winokur, Andy, M.D. 1979-1982 Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA

Gentry, W. Doyle, Ph.D. 1980-1983 Professor of Psychiatry & Behavioral Science, University of Texas Medical Branch, Galveston, TX

Kramer, Milton, M.D. 1980-1983 Assistant Chief, Psychiatry Service, VA Medical Center, Cincinnati, OH

Maxim, Peter E., M.D., Ph.D. 1980-1983 Associate Professor of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA

Merit Review Board for Cardiovascular Studies

Dodge, Harold T., M.D. 1972-1975 Professor of Medicine, University of Washington School of Medicine, Seattle, WA
Chairman 1972-1975

Parmley, William W., M.D. 1975-1978 Professor of Medicine, University of California School of Medicine, San Francisco, CA
Chairman, 1976-1978

Pitt, Bertram, M.D. 1978-1981 Professor of Medicine, University of Michigan School of Medicine, Ann Arbor, MI
Chairman, 1979-1981

Abboud, Francois M., M.D. 1972-1975 Professor of Medicine, University of Iowa School of Medicine, Iowa City, IA

Angell, William W., M.D. 1972-1975 Chief, Cardiovascular Surgery, Santa Clara Valley Medical Center, San Jose, CA

Cohn, Jay N., M.D. 1972-1975 Chief, Hypertension and Clinical Hemodynamics Research, VA Hospital, Washington, DC, later Professor of Medicine, University of Minnesota School of Medicine, Minneapolis, MN

Dammann, J. Francis, Jr., M.D. 1972-1975 Director of Pediatric Cardiology Research, University of Virginia School of Medicine, Charlottesville, VA

Fozzard, Harry A., M.D. 1972-1975 Professor of Medicine and Physiology, University of Chicago School of Medicine, Chicago, IL

Luchi, Robert J., M.D. 1972-1975 Chief, Medical Service, VA Hospital, Houston, TX

Mitchell, Jere H., M.D. 1972-1975 University of Texas, Southwestern Medical School, Dallas, TX

Ross, Richard S., M.D. 1972 Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Tarazi, Robert C., M.D. 1972-1975 Staff Member, Research Division, Cleveland Clinic, Cleveland, OH

Thomas, Wilbur A., M.D. 1972-1975 Professor of Pathology, Albany Medical College, Albany NY

Wallace, Andrew G., M.D. 1972-1975 Professor of Medicine, Duke University Medical School, Durham, NC

Zimmerman, Ben George, Ph.D. 1972-1975 Associate Professor of Pharmacology, University of Minnesota Medical School, Minneapolis, MN

Frohlich, Edward D., M.D. 1974-1977 Vice President for Research and Education, Alton Ochsner Medical Foundation, New Orleans, LA

Harrison, Donald C., M.D. 1975-1978 Professor of Medicine, Stanford University School of Medicine, Stanford, CA

Nies, Alan S., M.D. 1975-1978 Associate Professor of Pharmacology and Medicine, Vanderbilt University School of Medicine, Nashville, TN

Boineau, John P., M.D. 1976-1979 Chief of Cardiology, VA Hospital, Augusta, GA

Knoebel, Suzanne B., M.D. 1976-1979 Staff Physician, VA Hospital, Professor of Medicine, Indiana University School of Medicine, Indianapolis, IN

Morad, Martin, Ph.D. 1976-1979 Associate Professor of Physiology, University of Pennsylvania School of Medicine, Philadelphia, PA

Rolett, Ellis L., M.D. 1976-1979 Chief, Cardiology Section, VA Center, Wadsworth, Los Angeles, CA, later Professor of Medicine, Dartmouth University Medical School, Hanover, NH

Gunnar, Rolf M., M.D. 1977-1980 Professor of Medicine, Loyola University Stritch School of Medicine, Maywood, IL

Sambhi, Mohinder P., M.D., Ph.D., 1977-1980 Chief, Hypertensive Division, VA Hospital, Sepulveda, CA

DeMaria, Anthony, M.D., 1978-1982 Associate Professor of Medicine, University of California School of Medicine, Davis, CA

Halushka, Perry V., M.D., Ph.D. 1978-1981 Associate Professor of Pharmacology and Medicine, Medical University of South Carolina, Charleston, SC

Herman, Michael V., M.D. 1978-1981 Chief, Division of Cardiology, Mt. Sinai School of Medicine, New York, NY, later New York Medical College, Valhalla, NY

Holt, John H. Jr., M.D. 1979-1982 Chief, Cardiology Section, VA Medical Center, Birmingham, AL

Horwitz, Lawrence D., M.D. 1979-1982 Professor of Medicine, University of Colorado School of Medicine, Denver, CO

Lazzara, Ralph, M.D. 1979-1982 Chief, Cardiovascular Section, VA Medical Center, Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, OK

Ullrick, William C., Ph.D. 1979-1982 Professor of Physiology, Boston University School of Medicine, Boston, MA

Douglas, Janice G., M.D. 1980-1983 Associate Professor of Medicine, Case Western University School of Medicine, Cleveland, OH

Kerber, Richard, M.D. 1980-1983 Professor of Medicine, University of Iowa School of Medicine, Iowa City, IA

Merit Review Board for Endocrinology

Cahill, George F., Jr., M.D. 1972-1975, Professor of Medicine, Harvard Medical School, Boston, MA
Chairman, 1972-1975

Raisz, Lawrence G., M.D. 1974-1977, Professor of Medicine, University of Connecticut School of Medicine, Farmington, CT
Chairman, 1974-1977

Lockwood, Dean, M.D. 1976-1979, Professor of Medicine, University of Rochester School of Medicine, Rochester, NY
Chairman, 1977-1979

Mulrow, Patrick, M.D. 1978-1981, Professor and Chairman, Department of Medicine, Medical College of Ohio, Toledo, OH
Chairman, 1979-1981

Doe, Richard, M.D., Ph.D. 1972-1975 Professor of Medicine, University of Minnesota School of Medicine, Minneapolis, MN

Heaney, R. P., M.D. 1972-1975 Vice President for Health Sciences, Creighton University, Omaha, NE

Hershman, Jerome, M.D. 1972-1975 Clinical Investigator, VA Hospital, Birmingham, AL, later Chief, Endocrinology, VA Wadsworth Hospital Center, Los Angeles, CA

Kipnis, David M., M.D. 1972-1975 Head, Endocrinology & Metabolism, later Chairman, Department of Medicine, Washington University School of Medicine, St. Louis, MO

Lipsett, Mortimer B., M.D. 1972-1975 Associate Scientific Director, NICHD, National Institutes of Health, Bethesda, MD

Nelson, Donald H., M.D. 1972-1975 Professor of Medicine, University of Utah School of Medicine, Salt Lake City, UT

Porte, Daniel, Jr., M.D. 1972-1975 Associate Chief of Staff, VA Hospital, Seattle, WA

Steiner, Donald F., M.D. 1972-1975 Professor of Biochemistry, University of Chicago, Chicago, IL

Utiger, Robert, M.D. 1972-1975 Associate Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA

Orth, David N., M.D. 1974-1977 Professor of Medicine, Vanderbilt University School of Medicine, Nashville, TN

Spritz, Norton, M.D. 1974-1977 Chief, Medical Service, VA Hospital, New York, NY

Melby, James C., M.D. 1975-1978 Professor of Medicine, Boston University School of Medicine, Boston, MA

Nuttall, Frank Q., M.D., Ph.D. 1975-1978 Chief, Endocrine and Metabolism Section, VA Hospital, Minneapolis, MN

Sussman, Karl, M.D. 1975-1978 Staff Physician, VA Hospital, and Professor of Medicine, University of Colorado School of Medicine, Denver, CO

Woeber, Kenneth A., M.D. 1975-1978 Professor of Medicine, University of California School of Medicine, San Francisco, CA

Anast, Constantine S., M.D. 1976-1979 Associate Chief of Staff for Research, VA Hospital, Columbia, MO

Horton, Richard, M.D. 1976-1979 Professor of Medicine, University of Southern California School of Medicine, Los Angeles, CA

Surks, Martin I., M.D. 1976-1979 Head, Division of Endocrinology and Metabolism, Montefiore Hospital Medical Center, Bronx, NY

Krieger, Dorothy T., M.D. 1977-1978 Professor of Medicine, Mt. Sinai School of Medicine, New York, NY

Lukert, Barbara P., M.D. 1977-1980 Associate Professor of Medicine, University of Kansas School of Medicine, Kansas City, KS

Reaven, Gerald M., M.D. 1977-1980 Medical Investigator, VA Hospital, Palo Alto, CA

Braverman, Lewis, M.D. 1978-1981 Professor of Medicine, University of Massachusetts School of Medicine, Worcester, MA

Solomon, Solomon S., M.D. 1978-1981 Chief, Endocrinology & Metabolism Section, VA Medical Center, Memphis, TN

Chase, Lewis R., M.D. 1979-1982 Chief, Unit 1, Medical Service, VA Medical Center, St. Louis, MO

Frohman, Lawrence A., M.D. 1979-1982 Director, Division of Endocrinology, Michael Reese Medical Center, Chicago, IL

Kourides, Ione A., M.D. 1979-1982 Member, Sloan-Kettering Cancer Center, New York, NY

Pollet, Robert J., M.D. 1979-1982 Assistant Chief, Endocrinology and Metabolism, VA Medical Center, Tampa, FL

Troen, Philip, M.D. 1979-1982 Department of Medicine, Montefiore Hospital, Pittsburgh, PA

Arnaud, Claude, M.D. 1980-1983 Chief of Endocrinology , VA Medical Center, San Francisco, CA

Blackard, William G., M.D. 1980-1983 Professor of Medicine, Medical College of Virginia, Richmond, VA

Merit Review Board for Gastroenterology

Trier, Jerry S., M.D. 1972-1975 Associate Professor of Medicine, Boston University School of Medicine, later Professor of Medicine, Harvard Medical School, Boston, MA
Chairman, 1972-1975

Kaplan, Marshall M., M.D. 1974-1977 Professor of Medicine, Tufts University School of Medicine, Boston, MA
Chairman, 1975-1977

Fallon, Harold J., M.D. 1976-1979 Professor & Chairman, Department of Medicine, Medical College of Virginia, Richmond, VA
Chairman, 1977-1979

Powell, Don W., M.D. 1977-1980 Professor of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC
Chairman, 1979-1980

Ostrow, J. Donald, M.D. 1979-1982 Chief, Gastroenterology Section, VA Medical Center (Lakeside), Chicago, IL
Chairman, 1980-1982

Benson, John A. Jr., 1972-1975 Professor of Medicine, University of Oregon Medical School, Portland, OR

Conn, Harold O., M.D. 1972-1975 Chief, Liver Disease Section, VA Hospital, West Haven, CT

Englert, Edwin, Jr., M.D. 1972-1975 Chief, Gastroenterology Service, VA Hospital, Seattle, WA

Gray, Gary M., M.D. 1972-1975 Associate Professor of Gastroenterology, Stanford University School of Medicine, Stanford, CA

McGuigan, James E., M.D. 1972-1975 Professor of Medicine, University of Florida College of Medicine, Gainesville, FL

Moody, Frank G., M.D. 1972-1975 Professor of Surgery, University of Utah Medical Center, Salt Lake City, UT

Palmer, Robert H., M.D. 1972-1975 Associate Professor, Dept. of Medicine, University of Chicago, Chicago, IL, later Adjunct Professor, The Rockefeller University, New York, NY

Pope, Charles E. II, M.D. 1972-1975 Chief, Gastroenterology Service, VA Hospital, Seattle, WA

Rubin, Walter M., M.D. 1972-1975 Professor of Medicine, The Medical College of Pennsylvania, Philadelphia, PA

Schoenfield, Leslie J., M.D., Ph.D. 1972-1973 Director, Gastroenterology, Cedars of Lebanon Hospital, Los Angeles, CA

Scheig, Robert, M.D. 1972-1975 Associate Dean, Regional Activities, Yale University School of Medicine, New Haven, CT, later Chief, Medical Service, VA Hospital, Newington, CT

Soergel, Konrad H., M.D. 1972-1975 Professor of Medicine, Milwaukee County General Hospital, Milwaukee, WI

Winship, Daniel H., M.D. 1972-1975 Associate Professor of Medicine, University of Missouri Medical Center, Columbia, MO

Hendrix, Thomas R., M.D. 1974-1977 Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD

Morrissey, John F., M.D. 1974-1977 Professor of Medicine, University of Wisconsin School of Medicine, Madison, WI

Phillips, Sidney F., M.D. 1974-1977 Associate Professor of Medicine, Mayo Medical School, Rochester, MN

Cohen, Sidney, M.D. 1975-1978 Associate Professor of Medicine, University of PA School of Medicine, Philadelphia, PA

Jones, Albert L., M.D. 1975-1978 Chief, Cell Biology Laboratory, VA Hospital, San Francisco, CA

Singleton, John, M.D. 1975-1978 Associate Professor of Medicine, University of Colorado Medical School, Denver, CO

Adibi, Siamak, M.D., Ph.D. 1976-1979 Chief, Gastroenterology & Nutrition, Montefiore Hospital, Pittsburgh, PA

Alpers, David H., M.D., 1976-1979 Professor of Medicine, Washington University School of Medicine, St. Louis, MO

Grundy, Scott M., M.D. 1976-1979 Chief, Metabolism Section, VA Hospital, San Diego, CA

Isenberg, Jon, M.D. 1976-1979 Chief, Gastroenterology Service, VA Center (Wadsworth), Los Angeles, CA

Giannella, Ralph A., M.D. 1977-1980 Chief, Gastrointestinal Section, VA Hospital, Lexington, KY

Gregory, Peter B., M.D. 1977-1980 Associate Professor of Medicine, Stanford University School of Medicine, Stanford, CA

Silverstein, Fred E., M.D. 1977-1980 Associate Professor of Medicine, University of Washington School of Medicine, Seattle, WA

Beeken, Warren L., M.D. 1978-1981 Professor of Medicine, University of Vermont School of Medicine, Burlington, VT

Behar, Jose, M.D. 1978-1981 Assistant Professor of Medicine, Rhode Island Hospital, Providence, RI

Ito, Susumu, Ph.D. 1978-1981 Professor of Anatomy, Harvard Medical School, Boston, MA

Hanson, Russell F., M.D. 1979-1982 Associate Professor of Medicine, University of Minnesota Medical School, Minneapolis, MN

Schedl, Harold P., M.D. 1979-1982 Professor of Medicine, University of Iowa College of Medicine, Iowa City, IA

Spenny, Jerry G., M.D. 1979-1982 Chief, Gastroenterology Research, VA Medical Center, Birmingham, AL

Binder, Henry J., M.D. 1980-1983 Professor of Medicine, Yale University School of Medicine, New Haven, CT

Goyal, Raj K., M.D. 1980-1983 Professor of Medicine, University of Texas Health Science Center, San Antonio, TX

Lester, Roger, M.D. 1980-1983 Professor of Medicine, University of Texas Health Science Center, Houston, TX

Jensen, Dennis M., M.D. 1980-1983 Staff Physician, Gastroenterology Section, VA Medical Center(Wadsworth), and Assistant Professor of Medicine, University of California School of Medicine, Los Angeles, CA

Merit Review Board for Hematology

Harrington, William J., M.D. 1972-1975 Professor of Medicine, University of Miami School of Medicine, Miami, FL
Chairman, 1972-1975

Haut, Arthur, M.D. 1974-1977 Professor of Medicine, University of Arkansas School of Medicine, Little Rock, AK
Chairman, 1975-1977

Allen, Robert H., M.D. 1975-1978 Associate Professor of Medicine, Washington University School of Medicine, St. Louis, MO, later Professor of Medicine, University of Colorado School of Medicine, Denver, CO
Chairman, 1977-1978

Harris, John W., M.D. 1977-1980 Professor of Medicine, Case Western Reserve School of Medicine, Cleveland, OH
Chairman, 1978-1980

Robinson, Stephen H., M.D. 1979-1982 Professor of Medicine, Harvard Medical School, Boston, MA
Chairman, 1980-1982

Conley, C. Lockard, M.D. 1972-1975 Professor of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD

Finch, Stuart C., M.D. 1972-1975 Professor of Medicine, Yale University School of Medicine, New Haven, CT

Hall, Charles A., M.D. 1972-1975, 1978-1981 Medical Investigator, VA Hospital, Albany, NY

Jaffe, Ernest, M.D. 1972-1975 Professor of Medicine, Albert Einstein College of Medicine, Bronx, NY

Kaplan, Manuel, M.D. 1972-1975 Chief, Hematology Section, VA Hospital, Minneapolis, MN

Masouredis, Serafeim, M.D., Ph.D. 1972-1975 Professor of Pathology, University of California School of Medicine, San Diego, CA

Spaet, Theodore H., M.D. 1972-1975 Head, Department of Hematology, Montefiore Hospital & Medical Center, Bronx, NY

Stohlman, Frederick, Jr., M.D. 1972-1975 Director of Medicine, Research & Hematology, St. Elizabeth's Hospital, Brighton, MA

Marcus, Aaron J., M.D. 1974-1977 Chief, Hematology Section, VA Hospital, New York, NY

Sheehy, Thomas W., M.D. 1974-1977 Chief, Medical Service, VA Hospital, Birmingham, AL

Bank, Arthur, M.D. 1975-1978 Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

Boggs, Dane R., M.D. 1975-1978 Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

Rosenfield, Richard E., M.D. 1975-1978 Professor of Pathology, Mount Sinai Medical School, New York, NY

Miller, Kent D., M.D., Ph.D. 1976-1979 Professor of Medicine, University of Miami School of Medicine, Miami, FL

Furie, Barbara C., Ph.D. 1977-1980 Assistant Professor of Medicine, Tufts University School of Medicine, Boston, MA

Shattil, Sanford J., M.D. 1977-1980 Chief, Hematology, VA Medical Center, Phildelphia, PA

Bove, Joseph R., M.D. 1978-1981 Professor of Laboratory Medicine, Yale University School of Medicine, New Haven, CT

Golde, David W., M.D. 1978-1980 Department of Medicine, University of California, Los Angeles, Los Angeles, CA

Kan, Yuet Wai, M.D. 1978-1981 University of California School of Medicine, San Francisco, CA

Johnson, Gerhard, M.D. 1980-1983 Hematology Section, VA Medical Center, Minneapolis, MN

Menache-Aronson, Doris, M.D. 1980-1983 Associate Director, Blood Services Laboratories, Bethesda, MD

Merit Review Board For Immunology

Plotz, Charles, M.D., Med.Sc.D. 1972-1975 Professor of Medicine, State University of New York School of Medicine Brooklyn, NY
Chairman, 1972-1975

Butler, Vincent P., Jr., M.D., 1974-1977 Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, NY
Chairman, 1975-1977

Gill, Thomas J., III, M.D. 1976-1979 Professor and Chairman, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA
Chairman, 1977-1979

Spitler, Lynn E., M.D. 1977-1980 Director, Laboratory of Cellular Immunology, Children's Hospital of San Francisco, San Francisco, CA
Chairman, 1979-1980

Ward, Peter A., 1979-1982 Professor and Chairman, Department of Pathology, University of Connecticut School of Medicine, Farmington, CT, later Professor and Chairman, Department of Pathology, University of Michigan School of Medicine, Ann Arbor, MI
Chairman, 1980-1982

Baum, John, M.D. 1972-1975 Professor of Medicine, University of Rochester School of Medicine, Rochester, NY

Bennett, J. Claude, M.D. 1972-1975 Professor of Medicine, University of Alabama School of Medicine, Birmingham, AL

Braun, William E., M.D. 1972-1975 Director of Research and Histocompatibility Laboratory, Cleveland Clinic, Cleveland, OH

Friou, George J., M.D. 1972-1975 Professor of Medicine University of Southern California School of Medicine, Los Angeles, CA

Hollingsworth, James W., M.D. 1979-1975 Professor of Medicine, University of Kentucky College of Medicine, Lexington, KY

Kaplin, Melvin H., M.D. 1972-1975 Cleveland Metropolitan General Hospital, Cleveland, OH

Reichlin, Morris, M.D. 1972-1975 Chief, Clinical Immunology, VA Hospital, Buffalo, NY

Talal, Norman, M.D. 1972-1975 Chief, Clinical Immunology and Arthritis, VA Hospital, San Francisco, CA

Hurd, Eric R., M.D. 1974-1977 Associate Professor of Medicine, University of Texas South Western Medical School, Dallas, TX

Rapaport, Felix T., M.D. 1974-1977 Professor of Surgery, New York University School of Medicine, New York, NY

Sharp, Gordon C., M.D. 1975-1978 Professor of Medicine, University of Missouri School of Medicine, Columbia, MO

Stroud, Robert, M., M.D. 1975-1978 Professor of Medicine, University of Alabama School of Medicine, Birmingham, AL

Yoo, Tai June, M.D. 1975-1978 Staff Physician, VA Hospital and Associate Professor of Medicine, University of Iowa College of Medicine, Iowa City, IA

Chess, Leonard, M.D. 1976-1980 Assistant Professor of Medicine, Harvard Medical School, Boston, MA, later Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, NY

Winchester, Robert, J., M.D. 1976-1979 Associate Professor of Immunology, Rockefeller University, New York, NY

Barnett, Eugene V., M.D. 1977-1980 Professor of Medicine, University of California School of Medicine, Los Angeles, CA

Kreider, John, W., M.D. 1977-1980 Associate Professor of Pathology, Pennsylvania State University College of Medicine, Hershey, PA

Monaco, Anthony P., M.D. 1977-1980 Associate Professor, later Professor, of Surgery, Harvard Medical School, Boston, MA

Gligli, Irma, M.D. 1978-1979 Professor of Dermatology and Experimental Medicine, New York University School of Medicine, New York, NY
Grant, J. Andrew, M.D. 1978-1981 Associate Professor of Medicine and Genetics, University of Texas Medical Branch, Galveston, TX

Schur, Peter H., M.D. 1978-1981 Associate Professor, later Professor of Medicine, Harvard Medical School, Boston, MA

Ferrone, Soldano, M.D. 1979-1982 Associate Member, Department of Molecular Immunology, Scripps Clinic and Research Foundation, La Jolla, CA

Rabin, Bruce S., M.D. 1980-1983 Associate Professor of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Rosenberg, Jerry C., M.D. 1980-1983 Professor of Surgery, Wayne State University School of Medicine, Detroit, MI

Stevens, Mary B., M.D. 1980 – 1983 Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Tubergen, David G., M.D. 1980-1983 Associate Professor of Pediatrics, University of Colorado School of Medicine, Denver, CO

Merit Review Board for Infectious Diseases

Jackson, George G., M.D. 1972-1975 Professor of Medicine, University of Illinois School of Medicine, Chicago, IL
Chairman, 1972-1975

Gorbach, Sherwood L., M.D. 1974-1977 Professor of Medicine, Tufts University School of Medicine, Boston, MA
Chairman, 1975-1977

Andriole, Vincent, M.D. 1975-1978 Professor of Medicine, Yale University School of Medicine, New Haven, CT
Chairman, 1977-1978

Mandell, Gerald L., MD. 1977-1980 Associate Professor, later Professor of Medicine, University of Virginia Medical School, Charlottesville, VA
Chairman, 1978-1980

Douglas, R. Gordon, Jr., M.D. 1979-1982 Professor of Medicine and Microbiology, University of Rochester School of Medicine, Rochester, NY
Chairman, 1980-1982

Couch, Robert, M.D. 1972-1975 Professor of Microbiology and Medicine, Baylor College of Medicine, Houston, TX

Des Prez, Roger, M.D. 1972-1975 Chief, Medical Service, VA Hospital, Nashville, TN

Finegold, Sydney, M.D. 1972-1975 Chief, Infectious Disease Section, VA Hospital (Wadsworth), Los Angeles, CA

Kass, Edward Harold, M.D. 1972-1975 Director, Channing Laboratory, Boston City Hospital, Boston, MA

Kunin, Calvin, M.D. 1972-1975 Chief, Medical Service, VA Hospital, Madison, WI

Remington, Jack S., M.D. 1972-1975 Associate Professor of Medicine, Stanford University School of Medicine, Palo Alto, CA

Sanders, W. Eugene, Jr., M.D. 1972-1975 Associate Professor of Medicine and Immunology, University of Florida School of Medicine, Gainesville, FL, later Professor and Chairman, Department of Medical Microbiology, Creighton University School of Medicine, Omaha NE

Allen, James C., M.D. 1974-1977 Professor of Medicine, State University of New York School of Medicine, Buffalo, NY

Medoff, Gerald, M.D. 1974-1977 Professor of Medicine, Washington University School of Medicine, St. Louis, MO

Alford, Robert H., M.D. 1975-1978 Chief, Infectious Disease Section, VA Hospital, Nashville, TN

Weissmann, Gerald, M.D. 1975-1978 Professor of Medicine, New York University School of Medicine, New York, NY

Kaye, Donald, M.D. 1976-1979 Professor and Chairman, Department of Medicine, Medical College of Pennsylvania, Philadelphia, PA

Stevens, Jack G., D.V.M., Ph.D. 1976-1979 Reed Neurological Research Center, University of California School of Medicine, Los Angeles, CA

Waldman, Robert H., M.D. 1976-1979 Professor and Chairman, Department of Medicine, University of West Virginia School of Medicine, Morgantown, WV

Abernathy, Robert S., M.D. 1977-1980 Professor of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR

Hirschman, Shalom Z., M.D. 1977-1980 Professor of Medicine, Mt. Sinai School of Medicine, New York, NY

Norden, Carl W., M.D. 1978-1981 Montefiore Hospital, Pittsburgh, PA

Phair, John P., M.D. 1978-1981 Professor of Medicine, Northwestern University Medical School, Chicago, IL

Sheagren, John N., M.D. 1978-1981 Chief, Medical Service, VA Medical Center, Ann Arbor, MI

Sparling, Philip F., M.D. 1979-1981 Professor of Medicine and Bacteriology, University of North Carolina School of Medicine, Chapel Hill, NC

Washington, John A. II, M.D. 1979-1982 Head, Clinical Microbiology Section, Mayo Clinic, Rochester, MN

White, Arthur Clinton, M.D. 1979-1982 Chief, Infectious Deseases Section, VAMC and Professor of Medicine, Indiana University School of Medicine, Indianapolis, IN

Apicella, Michael A., M.D. 1980-1983 Professor of Medicine, University of Nevada School of Medicine, Reno, NV

Bennett, John E., M.D. 1980-1983 Head, Clinical Mycology Section, National Institute for Allergy and Infectious Diseases, Bethesda, MD

Clark, Robert A., M.D. 1980-1983 Associate Professor of Medicine, Boston University School of Medicine, Boston, MA

Merit Review Board for Nephrology

Schreiner, George E., M.D. 1972-1975 Professor of Medicine, Georgetown University School of Medicine, Washington, DC
Chairman, 1972-1975

Suki, Wadi N., M.D. 1974-1977 Professor of Medicine, Baylor College of Medicine, Houston, TX
Chairman, 1975-1977

Kirkendall, Walter M., M.D. 1975-1978 Professor of Medicine, University of Texas Medical School, Houston, TX
Chairman, 1977-1978

Hayslett, John P., M.D. 1976-1979 Associate Professor of Medicine, Yale University School of Medicine, New Haven, CT
Chairman, 1978-1979

Kjellstrand, Carl M., M.D. 1978-1981 Professor of Medicine and Surgery, University of Minnesota School of Medicine, Minneapolis, MN
Chairman, 1979-1981

Eknoyan, Garabed, M.D. 1972-1975 Staff Physician, VA Hospital, Houston, TX

Galletti, Pierre M., M.D. 1972-1975 Professor of Medicine, Biology & Medical Science, later Vice President for Biology and Medicine, Brown University, Providence, RI

Kountz, Samuel, M.D. 1972-1975 Associate Professor of Surgery, University of California School of Medicine, San Francisco, CA, later Chairman, Dept. of Surgery, State University of New York College of Medicine, Brooklyn, NY

Lavender, A. R., M.D. 1972-1975 Chief, Renal Section, VA Medical Center, Hines, IL

Ogden, David A., M.D. 1972-1975 Chief, Renal Section, VA Medical Center, Tucson, AZ

Seldin, Donald W., M.D. 1972-1973 Professor of Medicine, The University of Texas, Southwestern Medical School, Dallas, TX

Robinson, Roscoe R., M.D. 1973-1976 Professor of Medicine, Duke University School of Medicine, Durham, NC

Coburn, Jack W., M.D. 1975-1978 Chief, Nephrology Section, VA Medical Center (Wadsworth), Los Angeles, CA

Friedman, Eli A., M.D. 1975-1978 Professor of Medicine, State University of New York School of Medicine, Brooklyn, NY

Vaamonde, Carlos A., M.D. 1975-1978 Chief, Nephrology Section, VA Medical Center, Miami, FL

Foulkes, Ernest C., M.D. 1976-1979 Professor of Environmental Health and Physiology, University of Cincinnati Medical School, Cincinnati, OH

Stein, Jay H., M.D. 1976-1978 Professor of Medicine, University of Texas Health Science Center, San Antonio, TX

Purkerson, Mabel L., M.D. 1977-1980 Associate Professor of Medicine, Washington University School of Medicine, St. Louis, MO

Hoyer, John R., M.D. 1978-1981 Associate Professor of Pediatrics, Harvard Medical School, Boston, MA

Massry, Shaul G., M.D. 1978-1981 Professor of Medicine, University of Southern California School of Medicine, Los Angeles, CA

Weinman, Edward J., M.D. 1978-1981 Chief, Renal Section, VA Medical Center, Houston, TX

Kurtzman, Neil A., M.D. 1979-1982 Professor of Medicine, University of Illinois School of Medicine, Chicago, IL

Navar, Luis G., Ph.D. 1979-1982 Professor of Physiology and Biophysics, University of Alabama Medical School, Birmingham, AL

Di Bona, Gerald F., M.D. 1980-1983 Chief, Medical Service, VA Medical Center, Iowa City, IA

Epstein, Murray, M.D. 1980-1983 Associate Director, Nephrology, VA Medical Center, Miami, FL

Merit Review Board for Neurobiology

Weiner, Norman, M.D. 1972-1975 Professor of Pharmacology, University of Colorado School of Medicine, Denver, CO
Chairman 1972-1975

Standaert, Frank G., M.D. 1974-1977 Chairman, Department of Pharmacology, Georgetown University School of Medicine and Dentistry, Washington, D.C.
Chairman 1975-1977

Glaser, Gilbert H., M.D. 1975-1978 Professor & Chairman, Department of Neurology, Yale University School of Medicine, New Haven, CT
Chairman 1977-1978

Anderson, Edmund G., Ph.D. 1976-1979 Professor and Chairman, Department of Pharmacology, University of Illinois College of Medicine, Chicago, IL
Chairman 1978-1979

Bass, Norman H., M.D. 1978-1981 Professor of Neurology, University of Virginia Medical School, Charlottesville, VA, later Professor and Chairman, Department of Neurology, University of Kentucky School of Medicine, Lexington, KY
Chairman, 1979-1981

Asbury, Arthur, M.D. 1972-1975 Chief, Neurology Service, VA Hospital, San Francisco, CA, later Professor and Chairman, Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA

Barondes, Samuel, M.D. 1972-1975 Professor of Psychiatry, University of California School of Medicine, San Diego, CA

Efron, Robert, M.D., 1972-1975 Associate Chief of Staff, Research and Education, VA Hospital, Martinez, CA and Professor of Neurology, University of California School of Medicine, Davis, CA

Ferrendelli, J.A., M.D. 1972-1975 Assistant Professor of Pharmacology and Neurology, Washington University Medical School, St. Louis, MO

Hollien, Harry, Ph.D. 1972-1975 Professor, Communication Sciences Laboratory, University of Florida, Gainesville, FL

Kornetsky, Conan, Ph.D. 1972-1975 Professor of Psychiatry (Psychology) and Pharmacology, Boston University School of Medicine, Boston, MA

Lajtha, Abel, Ph.D. 1972-1975 N.Y. State Research Institute for Neurochemistry and Drug Addiction, Dept. of Mental Hygiene, State of N.Y., Ward's Island, N.Y.

Quarton, Gardner C., M.D. 1972-1975 Director, Mental Health Research Institute, The University of Michigan, Ann Arbor, MI

Segundo, Jose P., M.D. 1972-1975 Department of Anatomy, University of California School of Medicine, Los Angeles, CA

Welch, Keasley, M.D. 1972-1975 Professor of Neurosurgery, Harvard Medical School, Boston, MA

Woodbury, Dixon M., M.D. 1972-1975 Professor of Pharmacology, University of Utah College of Medicine, Salt Lake City, UT

Ziegler, Dewey, M.D. 1972-1975 Professor of Medicine and Neurology, University of Kansas School of Medicine, Kansas City, KS

Chow, Kao Liang, Ph.D. 1974-1977 Professor of Neurology, Stanford University School of Medicine, Palo Alto, CA

Teas, Donald C., Ph.D. 1974-1977 Professor, Department of Speech, Communications Sciences Laboratory, University of Florida, Gainesville, FL

Lasek, Raymond J., Ph.D. 1975-1978 Associate Professor of Anatomy, Case Western Reserve University School of Medicine, Cleveland, OH

O'Reilly, Sean, M.D. 1975-1978 Professor of Neurology, The George Washington University School of Medicine, Washington, DC

Rosomoff, Hubert, M.D. 1975-1978 Professor and Chairman, Department of Neurological Surgery, University of Miami School of Medicine, Miami, FL

Alksne, John F., M.D. 1976-1979 Professor of Neurosurgery, University of California School of Medicine, San Diego, CA

Hogan, Edward L., M.D. 1976-1979 Professor and Chairman, Department of Neurology, Medical University of South Carolina, Charleston, SC

Kornfeld, Mario, M.D. 1976-1979 Associate Professor of Pathology, University of New Mexico School of Medicine, Albuquerque, NM

Zomzely-Neurath, Claire E., D.Sc. 1976-1979 Assistant Member, Department of Biochemistry, Roche Institute for Molecular Biology, Nutley, NJ

Kennedy, Thelma T., Ph.D. 1977-1980 Professor of Physiology and Biophysics, University of Washington School of Medicine, Seattle, WA

Killam, Eva K., Ph.D. 1977-1978 Professor of Pharmacology, University of California School of Medicine, Davis, CA

Mirsky, Allan F., Ph.D. 1977-1980 Professor of Psychiatry and Neurology, Boston University School of Medicine, Boston, MA

Viemeister, Neil, Ph.D. 1977-1980 Associate Professor of Psychology, University of Minnesota, Minneapolis, MN

Forman, David S., Ph.D. 1978-1981 Naval Medical Research Institute, National Naval Medical Center, Bethesda, MD

Grossman, Robert G., M.D. 1978-1981 Professor of Neurosurgery, University of Texas Medical Branch at Galveston, Galveston, TX

Seiden, Lewis S., Ph.D. 1978-1981 Professor of Pharmacology and Physiological Science, University of Chicago School of Medicine, Chicago, IL

Gonatas, Nicholas K., M.D. 1979-1982 Professor of Pathology, University of Pennsylvania School of Medicine, Philadelphia, PA

Mayer, Richard F., M.D. 1979-1982 Acting Chairman, Department of Neurology, University of Maryland School of Medicine, Baltimore, MD

North, Richard A., M.D. 1979-1982 Associate Professor of Pharmacology, Stritch School of Medicine, Loyola University, Maywood, IL

Passonneau, Janet V., Ph.D. 1979-1982 Chief, Laboratory of Neurochemistry, NINCDS, National Institutes of Health, Bethesda, MD

Sypert, George, M.D. 1979-1982 Staff Neurologist, VA Medical Center, and Associate Professor, later Professor, of Neurosurgery and Neurosciences, University of Florida School of Medicine, Gainesville, FL

Henn, Fritz A., M.D., Ph.D. 1980-1983 Associate Professor of Psychiatry, University of Iowa School of Medicine, Iowa City, IA

MacDonald, Robert L., M.D., Ph.D. 1980-1983 Associate Professor of Neurology, University of Michigan School of Medicine, Ann Arbor, MI

Moushegian, George, Ph.D. 1980-1983 Director, Callier Center for Communication Disorders, Dallas, TX

Merit Review Board For Oncology

Hall, Thomas C., M.D. 1972-1975 Professor of Medicine and Pharmacology, University of Rochester School of Medicine and Dentistry, Rochester, NY, later, University of Southern California Cancer Center, Los Angeles, CA
Chairman, 1972-1975

Goldenberg, David, M.D., Sc.D. 1974-1977 Professor of Pathology, University of Kentucky School of Medicine, Lexington, KY
Chairman, 1975-1977

Hollinshead, Ariel, Ph.D. 1976-1979 Professor of Medicine, George Washington University School of Medicine, Washington, DC
Chairman, 1977-1979

Neiderhuber, John E. M.D. 1978-1981 Associate Professor of Surgery and Microbiology, University of Michigan School of Medicine, Ann Arbor, MI
Chairman, 1979-1981

Greenwald, Peter, M.D. 1972-1975 Director, Cancer Control Bureau, New York State Dept. of Health, Albany, NY

Hammond, William G., M.D. 1972-1975 Chief, Clinical Investigations Branch, Division of Cancer Grants, National Cancer Institute, Bethesda, MD, later Chief of Staff, VA Hospital, Sepulveda, CA

Loeb, Virgil, Jr., M.D. 1972-1975 Associate Professor of Clinical Medicine, Washington University School of Medicine, St. Louis, MO

Morton, Donald, M.D. 1972-1975 Chief, Surgical Service, VA Hospital, Sepulveda, CA

Nickson, James J., M.D. 1972-1975 Chairman, Radiation Therapy, Michael Reese Hospital, Chicago, IL, later Professor of Radiology, University of Tennessee School of Medicine, Memphis, TN

Parry, William L., M.D. 1972-1975 Chief, Urology Service, VA Hospital, Oklahoma City, OK

Selawry, Oleg, M.D. 1972-1975 Chief, NCI-VA Medical Oncology Service, VA Hospital, Washington, DC

Sherwin, Russell P., M.D. 1972-1975 Professor of Pathology, University of Southern California School of Medicine, Los Angeles, CA

Wolberg, William, M.D. 1972-1975 Professor of General Surgery and Clinical Oncology, University of Wisconsin School of Medicine, Madison, WI

Berg, John W., M.D. 1974-1977 Professor of Preventive Medicine, University of Iowa College of Medicine, Iowa City, IA

Gittes, Ruben F., M.D. 1974-1977 Professor of Urological Surgery, Harvard Medical School, Boston, MA

Fink, Mary A., Ph.D. 1975-1978 Acting Associate Director, Research Program, National Institutes of Health, Bethesda, MD

Gutmann, Helmut R., M.D. 1975-1978 Biochemist, VA Hospital, Minneapolis, MN

Nathanson, Larry, M.D. 1975-1978 Professor of Medicine, Tufts University School of Medicine, Boston, MA

Talley, Robert W., M.D. 1975-1978 Chief, Division of Oncology, Henry Ford Hospital, Detroit, MI

Bowen, James M., M.D., Ph.D. 1976-1979 Professor of Virology, M.D. Anderson Hospital, Houston, TX

Mihich, Enrico, M.D. 1976-1979 Director, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY

Perez, Carlos A., M.D. 1976-1979 Professor of Radiology, Washington University School of Medicine, St. Louis, MO

Fudenberg, Hugh H., M.D. 1977-1980 Professor and Chairman, Department of Basic and Clinical Immunology, Medical University of South Carolina, Charleston, SC

Goldstein, Allen L., Ph.D. 1977-1980 Professor of Biochemistry, University of Texas Medical Branch, Galveston, TX

Rosen, Fred, Ph.D. 1977-1980 Associate Director, Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, NY

Yesner, Raymond, M.D. 1977-1980 Chief Laboratory Service, VA Hospital, West Haven, CT

Yonemoto, Robert H., M.D. 1977-1980 Department of General and Oncological Surgery, City of Hope National Medical Center, Duarte, CA

Cohen, Martin H., M.D. 1978-1981 Assistant Chief, NCI-VA Medical Oncology Branch, VA Medical Center, Washington, DC

Lijinsky, William, Ph.D. 1978-1980 Director, Chemical Carcinogenesis, Frederick Cancer Research Center, Frederick, MD

Lippman, Marc E., M.D. 1978-1981 Head, Medical Breast Cancer Section, National Cancer Institute, National Institutes of Health, Bethesda, MD

Lopez, Diana M., Ph.D. 1979-1982 Associate Professor of Microbiology, University of Miami Medical School, Miami, FL

Parker, Robert G., M.D. 1979-1982 Professor of Radiology, University of California School of Medicine, Los Angeles, CA

Gale, Glen R., Ph.D. 1980-1983 Pharmacologist, VA Medical Center, Charleston, SC

Hellstrom, Karl E., M.D. 1980-1983 Program Head, Division of Tumor Immunology, Fred Hutchinson Cancer Research Institute, Seattle, WA

Heppner, Gloria H., Ph.D. 1980-1983 Chairman, Department of Immunology, Michigan Cancer Foundation, Detroit, MI

Hilf, Russell, Ph.D. 1980-1983 Professor of Biochemistry, University of Rochester School of Medicine, Rochester, NY

Reddy, Janardan K., M.D. 1980-1983 Professor of Pathology, Northwestern University Medical School, Chicago, IL

Merit Review Board for Oral Biology (1972-1975)

Sharry, John J., D.M.D. 1972-1975 Dean, Medical University of South Carolina College of Dental Medicine, Charleston, SC Chairman 1972-75

Boyne, Philip J., D.D.S. 1972-1975 Professor and Chairman of Oral Surgery, University of California, Center for the Health Sciences, Los Angeles, CA

Hefferen, John J., Ph.D. 1972-1975 Director, Division of Biochemistry, American Dental Association, Chicago, IL

Loiselle, Raymond J., D.D.S. 1972-1975 Chief, Dental Service, VA Hospital, Tampa, FL

MacKenzie, Richard S., D.D.S., Ph.D. 1972-1975 Professor of Dental Education, University of Florida College of Dentistry, Gainesville, FL

Person, Philip, D.D.S., Ph.D. 1972-1975 Medical Investigator, VA Hospital, Brooklyn, N.Y.

Schiffman, Elliott, Ph.D. 1972-1975 Biochemist, Laboratory of Biochemistry, National Institute of Dental Research. Bethesda, MD

Merit Review Board for Respiration

Boren, Hollis C., M.D. 1972-1975 Chief, Pulmonary Disease Section, VA Medical Center, Wood, WI later Medical Investigator, VA Medical Center, Tampa, FL
Chairman, 1972-1975

Snider, Gordon L., M.D. 1975-1978 Chief, Pulmonary Disease Section, VA Medical Center, Boston, MA
Chairman, 1976-1978

Cohen, Allen B., M.D., Ph.D. 1977-1980 Professor of Medicine, Temple University School of Medicine, Philadelphia, PA
Chairman, 1978-1979

Wahrenbrock, Eric A., M.D. 1977-1980 Associate Professor of Anesthesia, University of California School of Medicine, San Diego, CA
Chairman, 1979-1980

Kaltreider, H. Benfer, M.D. 1978-1981 Chief, Respiratory Care, VA Medical Center, San Francisco, CA
Chairman, 1980-1981

Kettel, Louis J., M.D. 1972-1975 Chief, Pulmonary Disease Section, VA Medical Center, Tucson, AZ

Kilburn, Kaye H., M.D. 1972-1975 Professor of Medicine, Duke University School of Medicine, Durham, NC later Chief, Pulmonary Disease, VA Hospital, Columbia, MO

Kleinerman, Jerome, 1972-1975 Head, Department of Pathology Research and Clinical Pathology, St. Lukes Hospital, Cleveland, OH

Laver, Myron B., M.D. 1972-1973 Dept. of Anesthesiology, Massachusetts General Hospital, Boston, MA

Liebow, Averill A., M.D. 1972-1975 Professor of Pathology, University of California School of Medicine, San Diego, CA

Loudon, Robert G., M.B., Ch.B. 1972-1975 Professor of Medicine, University of Cincinnati School of Medicine, Cincinnati, OH

Ross, Joseph C., M.D. 1972-1975 Professor of Medicine, later Chairman, Department of Medicine, Medical University of South Carolina, Charleston, SC

Said, Sami I., M.D. 1972-1975 Chief, Pulmonary Disease Section, VA Medical Center, Dallas, TX

Hamilton, Lyle E., Ph.D. 1974-1977 Principal Scientist, VA Medical Center, Wood, WI

Marshall, Bryan E., M.D. 1974-1977 Professor of Anesthesiology, University of Pennsylvania School of Medicine, Philadelphia, PA

Sharp, John T., M.D. 1974-1977 Program Director, Pulmonary Disease, VA Medical Center, Hines, IL

Cross, Carroll E., M.D. 1975-1978 Associate Professor of Medicine and Human Physiology, University of California School of Medicine, Davis, CA

Daly, Walter J., M.D. 1976-1979 Professor & Chairman, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN

Greenberg, S. Donald, M.D. 1976-1979 Professor of Pathology, Baylor College of Medicine Texas Medical Center, Houston, TX

Petty, Thomas L., M.D. 1976-1979 Professor of Medicine, University of Colorado School of Medicine, Denver, CO

Menkes, Harold A., M.D. 1977-1980 Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Cherniak, Neil S., M.D. 1978-1981 Chief, Pulmonary Section, VA Medical Center, Cleveland, OH

Gold, Warren M., M.D. 1978-1979 Professor of Medicine, University of California School of Medicine, San Francisco, CA

Massaro, Donald J., M.D. 1978-1981 Medical Investigator, VA Medical Center, and Professor of Medicine and Physiology, University of Miami School of Medicine, Miami, FL

Eldridge, Frederic, M.D. 1979-1982 Professor of Medicine and Physiology, University of North Carolina School of Medicine, Chapel Hill, NC

Hayes, John A., M.D. 1979-1982 Associate Director, Mallory Institute of Pathology, Boston, MA

Lieberman, Jack, M.D. 1979-1982 Chief, Respiratory Disease Section, VA Medical Center, Sepulveda, CA

Matthay, Richard A., M.D. 1979-1982 Associate Professor of Medicine, Yale University School of Medicine, New Haven, CT

Cheney, Frederick W., Jr., M.D. 1980-1983 Professor of Anesthesiology, University of Washington School of Medicine, Seattle, WA

Last, Jerold A., M.D. 1980-1983 Professor of Medicine, University of California School of Medicine, Davis, CA

Weil, John V., M.D. 1980-1983 Professor of Medicine, University of Colorado School of Medicine, Denver, CO

Merit Review Board in Surgery

Eiseman, Ben A., M.D. 1972-1974 Professor of Surgery, University of Colorado School of Medicine, Denver, CO
Chairman 1972-1973

Bryant, Lester, M.D. 1972-1975 Professor of Surgery, University of Kentucky School of Medicine, Lexington, KY, later Professor of Surgery, Louisiana State University School of Medicine, New Orleans, LA
Chairman 1973-1975

Siegel, John H., M.D. 1975-1978 Professor of Surgery, State University of New York School of Medicine, Buffalo, NY
Chairman 1975-1978

Condon, Robert E., M.D. 1977-1980 Chief, Surgical Service, VA Center, Wood, WI
Chairman 1978-1980

Hechtman, Herbert B., M.D. 1978-1981 Associate Professor of Surgery, Harvard Medical School, Boston, MA
Chairman 1980-1981

Artz, Curtis P., M.D. 1972-1975 Professor of Surgery, Medical University of South Carolina, Charleston, SC

Blaisdell, F. William, M.D. 1972-1975 Professor of Surgery, University of California School of Medicine, San Francisco, CA

DelGuercio, Louis, M.D. 1972-1975 Director of Surgery, St. Barnabas Medical Center, Livingston, NJ

Dudrick, Stanley J., M.D. 1972-1975 Associate Professor of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, later Professor and Chairman, Department of Surgery, University of Texas School of Medicine, Houston, TX

Egdahl, Richard H., M.D. 1972-1974 Professor of Surgery, Boston University School of Medicine, Boston, MA

Menguy, Rene B., M.D., Ph.D. 1972-1975 Professor of Surgery, University of Rochester School of Medicine, Rochester, NY

Merendino, K. Alvin, M.D., Ph.D. 1972-1975 Professor of Surgery, University of Washington School of Medicine, Seattle, WA

Orloff, Marhsall J., M.D., Ph.D. 1972-1975 Professor of Surgery, University of California School of Medicine, San Diego, CA

Powers, Samuel R.,Jr., M.D., D.Sc. 1972-1975 Professor of Surgery, later Professor and Chairman, Department of Surgery, Albany Medical College of Union University, Albany, NY

Schumer, William, M.D. 1972-1975 Chief of Surgery, VA Hospital (West Side), Chicago, IL

Simmons, Richard L., M.D. 1972-1975 Associate Professor, later Professor, of Surgery and Microbiology, University of Minnesota School of Medicine, Minneapolis, MN

Wolf, James, M.D. 1972-1973 Chief of Surgery, VA Hospital, Richmond, VA

DenBesten, Lawrence, M.D. 1974-1977 Chief, Surgical Service, VA Hospital, Iowa City, IA

Kouchoukos, N.T., M.D. 1974-1977 Associate Professor of Surgery, University of Alabama School of Medicine, Birmingham, AL

Sherman, Roger T., M.D. 1974-1977 Professor and Chairman, Department of Surgery, University of South Florida College of Medicine, Tampa, FL

Skillman, John J., M.D. 1974-1977 Department of Surgery, Harvard Medical School, Boston, MA

Collins, John A., M.D. 1975-1978 Professor of Surgery, Stanford University School of Medicine, Stanford, CA

Peters, Richard, M.D. 1975-1978 Professor of Surgery, University of California School of Medicine, San Diego, CA

Starzl, Thomas E., M.D., Ph.D. 1975-1978 Professor and Chairman, Department of Surgery, University of Colorado School of Medicine, Denver, CO

Storer, Edward H., M.D. 1975-1978 Chief, Surgical Service, VA Hospital, West Haven, CT

Sumner, David S., M.D. 1975-1978 Professor of Surgery, Southern Illinois School of Medicine, Springfield, IL

Alexander, J. Wesley, M.D. 1976-1979 Director, Transplantation Division, University of Cincinnati Medical Center, Cincinnati, OH

McDonald, John C., M.D. 1976-1979 Professor of Surgery, Tulane University School of Medicine, New Orleans, LA, later Professor and Chairman, Department of Surgery, Louisiana State University School of Medicine, Shreveport, LA

Norman, John C., M.D. 1976-1979 Director, Cardiovascular Surgery Research Laboratories, Texas Heart Institute, Houston, TX

Paulson, David F., M.D. 1976-1979 Director, Urology Research, VA Hospital, and Associate Professor of Urologic Surgery, Duke University School of Medicine, Durham, NC

Williams, G. Melville, M.D. 1976-1979 Professor of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD

Schloerb, Paul R., M.D. 1977-1980 Professor of Surgery, University of Kansas School of Medicine, Kansas City, KS, later Professor of Surgery, University of Rochester School of Medicine, Rochester, NY

Tyers, G. Frank O., M.D. 1977-1980 Professor of Surgery, University of Texas Medical Branch, Galveston, TX, later Division of Cardiovascular and Thoracic Surgery, Vancouver General Hospital, Vancouver, BC

Way, Lawrence W., M.D. 1977-1980 Chief, Surgical Service, VA Hospital, San Francisco, CA

Barnes, Robert W., M.D. 1978-1981 Chief, Vascular Surgery, VA Medical Center, Richmond, VA

Kinney, John M., M.D. 1978-1981 Professor of Surgery, Columbia University College of Physicians and Surgeons, New York, NY

Moss, Gerald S., M.D. 1978-1981 Professor of Surgery, University of Chicago School of Medicine, Chicago, IL

Thompson, Roby C., Jr., M.D. 1978-1980 Professor and Chairman, Department of Orthopedic Surgery, University of Minnesota School of Medicine, Minneapolis, MN

Hakala, Thomas R., M.D. 1979-1982 Chief, Urological Surgery, VA Medical Center and Professor of Urological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA

Jonasson, Olga M., M.D. 1979-1982 Professor of Surgery, Department of Surgery, Cook County Hospital, Chicago, IL

Nichols, Ronald L., M.D. 1979-1982 Professor of Surgery, Tulane University School of Medicine, New Orleans, LA

Walker, William E., M.D. 1979-1982 Assistant Professor of Surgery, University of Texas Medical Science Center, Houston, TX

Jones, R. Scott, M.D. 1980-1983 Assistant Chief of Surgery, VA Medical Center, Durham, NC

Matthews, Larry S., M.D. 1980-1983 Professor of Orthopedic Surgery, University of Michigan School of Medicine, Ann Arbor, MI

Nicholas, Gary G., M.D. 1980-1983 Associate Professor of Surgery, Pennsylvania State University School of Medicine, Hershey, PA

Sheldon, George F., M.D. 1980-1983 Professor of Surgery, University of California School of Medicine, San Francisco, CA

Appendix IIm. NAS-NRC Committees Planning and Advising VA on Rehabilitation Research

1/30–2/1/45	Meeting at Thorne Hall, Northwestern University, sponsored by Panel on Amputations, Committee on Surgery, Division of Medical Sciences, NRC-NAS
April–Autumn 1945	Committee on Prosthetic Devices, jointly under Division of Medical Sci. and Division of Engineering & Industrial Research, NRC-NAS.
Jan 1944–Nov 1945	Committee on Sensory Devices, organized by OSRD, transferred to NRC Oct, 1945.
Nov 1945–Nov 1946	Board for Prosthetic and Sensory Devices with two Committees: Committee on Prosthetic Devices and Committee on Sensory Devices
Nov 1946–July 1947	Committee on Artificial Limbs and Committee on Sensory Devices, under the Division of Engineering and Industrial Research, NRC-NAS.
July, 1947–1955	Advisory Committee on Artificial Limbs. (Contracting now to be done directly by VA and by Armed Services rather than by NRC.) General F.S. Strong, Jr. Executive Director Identified research needs. Recommended research projects to the VA Used funds to tool up new projects Procured models to "prime the pump" Organized and held workshops and meetings Prepared reports Exhibits at scientific meetings Published journal Artificial Limbs from 1954–1972, 5000 circulation
Nov 1948–1954	Committee on Sensory Devices now in Division of Anthropology and Psychology.
1955–1959	Advisory Committee on Artificial Limbs became Prosthetics Research Board with two Committees: Committee on Prosthetics Research and Development and Committee on Prosthetics Education and Information, again jointly under Division of Medical Sciences and Division of Engineering and Industrial Research, NRC-NAS.
1959–1976	Committee on Prosthetics Research and Development, Division of Engineering and Industrial Research, NRC-NAS.

1964–1976	New Subcommittee on Sensory Aids established at VA request under Committee on Prosthetics Research and Development.

Appendix III. Selected *Technical Bulletins*

1946

Heinle, R., "Folic acid in the treatment of macrocytic anemias"
Pinner, M., "The bacteriological diagnosis of pulmonary tuberculosis"
Simmons, J., "Treatment of malaria"
Leifer, W., Padget, P., Pillsbury, D., & Johnson, B., "The management of syphilis"
Means, J., "New methods of treating thyrotoxicosis"
Walker, A., "Recent changes in the composition of commercial penicillin"
Walker, A., "The treatment of poisoning by arsenicals and mercury with BAL"
White, J., "Surgery of the autonomic nervous system"
Walker, A., "The fractionation of plasma proteins"

1947

Lennox, W., "The treatment of the epileptic veteran"
Frank, J., "Management of emotional reactions in patients with somatic disease"
Homans, J., "Venous thrombosis in the lower limbs, its present day treatment"
Leifer, W., "The medical management of neurosyphilis"
Elsom, K., "Amebiasis with special reference to its late complications"
Ruffin, J., "Vagotomy in the treatment of peptic ulcer"
Romansky, M., "The current status of penicillin therapy"
Streptomycin Committee, VACO, "A preliminary statement concerning the effects of streptomycin upon tuberculosis in man"
Most, H. "Clinical aspects and treatment of the more common intestinal parasites of man"
Most, H., "Schistosomiasis in the veteran"
Ozarin, L., "Electric shock therapy"
Alexander, H., "The pathogenesis of allergic disorders and the pronciples of their management"
Capps, R., "The present status of viral hepatitis, with particular reference to chronic and residual forms"
Duncan, G., "The management of diabetes mellitus"
Campbell, P., "The diagnosis and treatment of acute and chronic external otitis"

1948

Owen, G., "Late residuals of primary coccidioidomycosis"
Bradford, F., "The diagnosis and treatment of intervertebral disk rupture"
Ebert, R., "The measurement of cardiac output"
Paster, S., "Shock therapies of the psychoses"
Shurley, J., and Bond, E., "Insulin shock therapy in schizophrenia"
Most, H., "Management of vivax malaria in the veteran"
DeGraff, A., "Management of cardiac failure"
Solomon, H., "Prefrontal leukotomy, an evaluation"
Bors, E., "Spinal cord injuries"
Hayman, J., "The measurement of renal function"

1949
Leifer, W., "The management of syphilis"
Leifer, W., "The medical management of neurosyphilis"
Spink, W., "Diagnosis and management of brucellosis (undulant fever) "
Dripps, R., "Spinal anesthesia for diagnosis, prognosis and therapy"
Strauss, M., "The biology of pernicious anemia"
Lyon, G., "Radioisotopes in medicine"
Riley, R., "The measurement of pulmonary function"
Schroeder, H., "Arterial hypertension"
Gootnik, A., "The use of digitalis, with special reference to its toxicity"
Comroe, J., "The mode of action of drugs upon the autonomic nervous system"
Rosenberg, E., "Rheumatoid arthritis, with especial reference to its treatment"
Wilbur, D., "The vitamins and vitamin deficiency disease"

1950
Florsham, P., & Thorn, G., "The diagnosis and treatment of adrenal cortical insufficiency"
Welt, L., & Seldin, D., "The pathologic physiology and treatment of edema"
Rhoads, C., "Present trends in cancer research, a general discussion"
Beck, C., "Treatment of cardiac arrest"
Elsom, K., "Chronic nonspecific ulcerative colitis"
Wortis, S., & Pfeffer, A., "The management of alcoholism"
Lyon, G., "Some aspects of medical planning in atomic warfare"
Wright, I., "The treatment of coronary thrombosis with myocardial infarction"
Canfield, N., Glorig, A., & Ansberry, M., "Audiology - the science of hearing"
Wagley, P., "A consideration of certain aspects of blood transfusions with particular reference to the clinical complications"

1951
Ruffin, J., "The management of peptic ulcer"
Ravdin, I., & Gimbel, N., "Parenteral protein nutrition"
Elsom, K., "The management of gastro-intestinal hemorrhage"
Baehr, G., & Levitt, M., "The diseases of collagen"
Isbell, H., "Acute and chronic barbiturate intoxication"
Beeson, P., "Fever of obscure origin"
Hanlon, C., "The surgical treatment of cardiovascular disease"
North, J., "Cancer and other tumors of the stomach"
Daniels, W., & MacMurray, F., "Differential diagnosis and management of pyogenic meningitis"
Lindsay, J., "The differential diagnosis of vertigo"
Longcope, W., "Sarcoidosis"

1952
Finland, M., "Pneumonia: present status of diagnosis and treatmen"
Peabody, F., "The care of the patient"
Rhodes, J., "Malignancy of the colon and rectum"

1953
Talbott, J., "Gout and gouty arthritis"
Machella, T., "Acute and chronic pancreatitis"
Frank, J., "Group psychotherapy"
Stanbury, J., & Means, J., "New methods of treating thyrotoxicosis"
Lorr, M., "Multidimensional scale for rating psychiatric patients 1. Hospital form"
Bennett, I., Jr., "Poisoning due to substances commonly substituted for ethyl alcohol"
Weir, J., "Gallstones"
Ozarin, L., "The care and treatment of the psychotic patient with tuberculosis"
Most, H., "Management of vivax malaria in the veteran"
Schwartz, S., "Clinical aspects of porphyrin metabolism"

1954
Kolff, W., "Dialysis in the treatment of uremia - artificial kidney and peritoneal lavage"
Bennett, I., "Bacteremia"
Hudson, P., "Benign and malignant tumors of the prostate gland"
Klatskin, G., "Leptospirosis"
Welt, L., "The pathogenesis and management of dehydration"
Schroeder, H., "The treatment of arterial hypertension"
Joyner, C., "Coronary atherosclerosis - pathogenesis and therapeutic implications"
Kossman, C., "Electrocardiography and vectorcardiography"
Strecker, E., "General principles of psychotherapy"
Doull, J., "Leprosy"

1955
Jones, R., Jr., "Medical management of patients with incurable cancer"
Howard, J., "Differential diagnosis and therapy of spontaneous hypoglycemia"
Pillsbury, D., "Topical and systematic therapy in diseases affecting the skin"
Maier, H., "Intrathoracic tumors"
Warren, R., "Recent advances in the surgery of arterial diseases"
Smith, H., "Notes on the history of renal physiology"

(Intentionally Blank)

Appendix IVa. Early research contracts approved by the Committee on Veterans Medical Problems

(Information extracted by the author from the minutes of the Committee on Veterans Medical Problems, archives of the National Academy of Science)

1947

Lennox, W.G., Cushing VA Hospital, Framingham, MA "VA Medical Problems" $75,000

Adler, D.L., University of Oregon, Eugene, V.A. Hospital, Roseburg, and V.A. Hospital, Portland, OR, "Nature of Schizophrenic Thought Processes" No funds requested

Walker, A. E., John Hopkins Hospital, "Posttraumatic Epilepsy Registry" $11,620

Moore, T.V., Catholic University of America, "Nature of Neuropsychiatric Breakdown" No funds requested

Brill, N.Q., N. P. Division, VACO "Follow-Up of Psychoneuroses in Veterans" $47,500

Brill, N.Q., N. P. Division, VACO "Follow-Up of Psychoses in Officer Veterans" $15,700

Menninger, K.A., Winter VA Hospital, Topeka, "Value of Finger Painting in N.P. Disorders" $20,644

Powermaker, F., N.P. Division, VACO, "Group Therapy in V.A. Hospitals and Clinics" $45,768

Woodhall, B., V.A. (Consultant on Peripheral Nerves) and Duke Medical School, Durham, NC, "Follow-Up Peripheral Nerve Injuries" $ 100,090, including:

White, J.C.	Boston Study Center	$13,200; renewed 1951 for $2,700.
Davis, L.	Chicago Study Center	$20,500, renewed 1951 for $5,000.
Grundfest, H.	New York's Study Center	$22,500
Lewey, F.H.	Philadelphia's Study Center	$21,340
Naffziger, H.	San Francisco's Study Center	$22,500

Elkin, D.C., Emory University School of Medicine and Emory University, Atlanta, GA, "Follow-Up of Traumatic Aneurysms and A-V Fistulae" $24,000

Woodhall, B, Duke Medical School, Durham, NC, "Neuropathology of Peripheral Nerve Injuries" $7,335

Most, H., New York University College of Medicine, Emory University, "Follow-Up of Schistosomiasis in Veterans" $3,450

Hayman, J.M., Western Reserve University, Cleveland, OH; Gordon, J.E., Harvard University, Boston, MA; Bang, F.B., John Hopkins University, Baltimore, MD; Palmer, W.L., University of Chicago Medical Ctr., Chicago, IL "Follow-up of Schistosomiasis Japonica Acquired in Military Service" $22,775

Burch, G.E. and DeBakey, M.E., Tulane University School of Medicine, New Orleans, LA, "Follow-Up of Arterial Injuries in Veterans" $78,950

Myers, J. A., University of Minn., Minneapolis, "Tuberculosis in Veterans" $3,000

Schwartz, H.G., Washington University, St. Louis, Mo., Barnes Hospital, St. Louis, MO, "EEG in Focal Epilepsy" $16,300

Turner, R.H, Tulane University, New Orleans, LA, "Liver Function Following Hepatitis" $20,500

Pollock, L.J., Veterans Administration Hospital, Hines, IL, Northwestern University, Chicago, "Spinal Cord Injury" $11,000

Michael, Max, Lawson Veterans Administration Hospital, Chamblee, GA, "Pathogenesis of Arthritis" $5,400

Neefe, J.R., University of Penn., Philadelphia, "Liver Function Following Hepatitis" $28,600

Barr, J.S., "Follow-Up Study of Fractured of Carpal Scaphoid" $20,500

Rapaport, D., Winter Veterans Administration Hospital, Topeka, KS, "Selection for Psychiatry Training" $23,595

Kelly, E.L., University of Michigan, Ann Arbor, MI, "Selection for Training in Clinical Psychology" $29,500

Carhart, R., Northwestern University, Evanston, IL, "Aural Rehabilitation" $17,825

Wolff, H.G., Veterans Administration Hospital #81, Bronx, NY, "Personality and stress in Epilepsy" $24,800

Wolff, H.G., Veterans Administration Hospital #81, Bronx, NY, New York Hosp., Institute of Psychological Research, Teachers' College, Columbia University (Contracting Institute Cornell University Medical College), "The Development of An Instrument that will Collect A large Body of Significant Medical and Psychiatric Data for Diagnostic and Prognostic Appraisal" $18,500

Haldeman, H.O., University of California Medical School, San Francisco, CA, "Experimental Study of Traumatic Lesions of Joints and Method of Their Surgical Repair" $5,320

Flanagan, J.C., "Preliminary Study of The Incidence of Psychoneurotic Disorders Among Former AAF Aircrew Candidates" $8,610

White, P.D., Massachusetts General Hospital, "Follow-Up Studies On Patients With Neurocirculatory Asthenia, Anxiety Neurosis, Effort Syndrome, and Allied States" No funds requested

Warren, R., “Follow-Up Study of War Wounds Of The Hands” $2,554

Wolff, H.G., Veterans Administration Hospital #81, Bronx, NY, “Studies on the Pathogenesis and Treatment of Myasthenia Gravis” $8,450

Kelly, F.P., “Post-Traumatic Osteomyelitis: Comparison of Recurrence Rate Following Two Forms of Treatment” $2,350.

Nesbitt, S., University of Minnesota School of Medicine, Veterans Administration Hospital, “Liver Function Status of World War II Veterans in Relation To Past Presence or Absence of Hepatitis or Its Sequelae” $26,750

Brown, J.R., Veterans Administration Hospital, Minneapolis, MN, “Rehabilitation of Chronic Neurologic Patients” $14,800 Revised 1949 as “Neurophysiological Studies in Neurological Disorder” $13,400

1947 applications not approved: 10, including 2 with VA participation.

1948

Lieby, G.M., Birmingham VA Hospital Van Nuys, CA, “Chemotherapy of Coccidioidomycosis” $20,900 Renewed in 1950 by Lack, A. for $28,200

Sternberg, T.H., “Mental Status and Treatment in Paresis” $10,000

Bender, M.B., New York University School of Medicine, “After Effects of Head Injuries In World War II (With Emphasis on Perceptual Function)” $6,150

Yater, W.M., “Life History of Coronary Artery Disease In Veterans” $6,500

Leiby, G.M., Birmingham VA Hospital, Van Nuys, CA, “A-Conjunctival Capillaroscopy, B-Plethysmograpy, C-Circulation Velocity, D-Vector-Cardiography” $11,996

Fulton, J.F., Yale University School of Medicine, New Haven, CT, “Physiological Basis Of The Operation of Frontal Lobotomy” $35,100

Bellows, J.G., “Effects of The Various Antibiotics On Experimental and Clinical Ocular Infections” $11,000

Beeson, P.B. and Michael, M., Emory University and Lawson VA Hospital, “Sarcoidosis” $21,460

Talbot, D.R., “EEG Studies In Relapsing Malaria and In Psychoses” Amount not recorded

Moore, R. A., Washington University, “Tumors Of The Testis” $10,700

Engleman, E. P., VA Hospital, San Francisco, CA, “Follow-up Studies In Rheumatic Fever In Veterans” $10,600

Winternitz, M.C., Yale University School of Medicine, “Etiology and Pathogenesis Of Cardiovascular Renal Disease” $14,700

Shumacker, H.B., Jr., Indiana University School of Medicine, “Paraplegia Research Unit” $26,142

Leiby, G.M., Birmingham VA Hospital, Van Nuys, CA, “Investigation of Antithyroid Activity of Certain Drugs” $3,900

Elkin, D.C., Grady Memorial Hospital and Emory University, Atlanta, GA, “Evaluation of the Use of Anticoagulants Particularly Heparin in the Therapy of Circulatory Insufficiency” $6,750

Bieter, R.N., University of Minnesota Veterans Administration Hospital, “Clinical Testing of Narcotic Drugs” $16,569

Taplin, G.V., Van Nuys, CA (Probably Birmingham VA Hospital), “Radioisotope Diagnosis” $3,974

Chaikoff, I.L., University of California Medical School, Berkeley, “Factors in Prevention of Liver Injury” $17,100

McGuire, J., Cardiac Laboratory, University of Cincinnati, Cincinnati, OH, “Cor Pulmonale and Related Pulmonary Physiology” $16,232

Weyrauch, H.M., University of California Medical School, San Francisco, CA , “Healing of the Prostatic Fossa after Transurethral Prostatectomy. The Pathogenesis of Prostatic Hypertrophy in the Dog” $1,620

Stewart, J.D., University of Buffalo Medical School, Buffalo, NY, “Physiological Adjustments to Hemorrhage and the Fate of the transfused Red Blood Cell” $26,700

Donahue, W.T., University of Michigan, Ann Arbor, MI, “Study of A2 Electronic Reader for the Blind” $15,600

Padget, P., John Hopkins University, Baltimore, MD; Webster, B., Cornell University School of Medicine, New York, NY, “The Natural History of Cardiovascular Syphilis” $15,478

Davis, H., Central Institute for the Deaf, St. Louis, MO, “Methods for Diagnosis of Impairment of Hearing and Application to Aural Rehabilitation” $11,716

1948 applications not approved: 19, including 6 with VA participation.

1949

Wuehrmann, A., Tufts Dental College, Boston, MA, “Improvements in Diagnosis of Periodontal and Periapical Involvements of Teeth” $15,140

Hampton, A.O., Walter Reed General Hospital, Garfield Memorial Hospital, Washington, DC, "Delayed Effects of One Million Volt Irradiation on Gastro-intestional Tract and on Testicular Tumors" $18,900

Blades, B., George Washington University Medical School, Washington, DC, "Studies of the Nerve Supply of the Human Lung with Particular Reference to the Physiology and Mechanism of Bronchoconstriction" $33,510

Decamp, P.T., Tulane University School of Medicine, "Experimental Methods for the Repair of Defects in Great Vessels" $1,762

Meschan, I., Veterans Administration Hospital, Little Rock, AK, "Microradiography, a Microscopic Radiographic Study of Tissues" $7,500

Jergesen, F.H., University of California Medical School, Materials Testing Laboratory College of Engineering, Ft. Miley Veterans Administration Hospital, San Francisco, CA, "Fractures of the Shafts of the Long Bones" $7,000

Schepens, C.L., Massachusetts Eye and Ear Infirmary, Boston, MA, "Examination Procedure and Treatment Methods of Retinal Detachment" $11,750

Tryon, R. C., Ballache, E. L., University of California, Berkeley, CA, "Research Survey of Some Social Psychological Correlates of Psychiatric Disorders" $20,990

Hudack, S. S., Columbia University College of Physicians and Surgeons, New York, NY, "To Study the Methods of Application of Plastic Materials in Reconstructive Surgery" $20,000

Nielson, J.M., Los Angeles VA Hospital Wadsworth General Hospital Brentwood Neuropsychiatric Hospital Domiciliary, "Evaluation of the Problem of Epilepsy in Veterans in the Los Angeles Area" $40,697

Kirk, P.L., University of California Medical School, Berkeley, CA, "Histochemistry of the Liver as Applied to Biopsy Material from Clinical Cases" $9,500

Beecher, H.K., Massachusetts General Hospital Boston, MA, "Role of Anesthesia in Production of Peripheral Vascular Impairment or Occlusion" $4,445

Long, C.N.H., Yale University School of Medicine New Haven, CT, "Characterization of Meningo-pneumonitis, a Virus of Psittacosis-lymphogranuloma venereum" $2,500

Marwin, R.M., University of North Dakota School of Medicine, Grand Forks, ND, "Ultrasonic Studies, Selective Filtrations and Differential Centrifugations of Pathogenic Fungi for the Purpose of Obtaining Diagnostic Antigens Plus Specific Antisera" $9,800

Simeone, F.A., Massachusetts General Hospital Boston, MA, "Autonomic Control of Renal Circulation" $3,000

Peyton, F.A., University of Michigan, Ann Arbor, "Determination of Physical Constants and Mechanical Characteristics in Dental Restorations" $18,600

1949 applications not approved: 19, including 7 with VA participation.

1950

Ingelfinger, F,. Evans Memorial Hospital and Massachusetts Memorial Hospital Boston, "The Effect of Drugs, Especially Sedatives, in Patients With Hepatic Disorder" $9,950

Hanger, F.M., Presbyterian Hospital, New York, NY, "Effect of Cortisone on Mesenchymal Derangements of the Liver" $1,700

Phillips, R.W., Indiana University School of Dentistry Indianapolis, IN, "Dimensional Change in Various Hydro-Colloids and Stones as Affected by Certain Manipulative Variables" $3,800

Randall, H.M., University of Michigan, Ann Arbor, "Adaptation of Infrared Spectroscopy to Bacteriological Work" $10,000

Freeman, S., Northwestern University Medical School and Veteran's Hospital Hines, IL, "Effects of Congestive Heart Failure on Renal Hemodynamics and Sodium Excretion" $7,480

Elkin, D.C., Emory University Hospital, GA; Churchill, E.D., Massachusetts General Hospital, Boston; De Takats, G., University of Illinois College of Medicine; Burch, G.E., Tulane University School of Medicine, "Investigation of Late Results in Individuals Who Sustained Trenchfoot, Immersion Foot, or Frostbite in World War II" $67,187

Vorwald, A.J., The Saranac Laboratory of The Edward L. Trudeau Foundation, Saranac, NY, "Influence of Cortisone Upon Chronic Inflammatory Disease of the Lung" $8,700

Adolph, W., Birmingham VA Hospital, Van Nuys, CA, "The Use of Microopulverized Radiopaques in X-Ray" No amount stated

Zieve, L., University of Minnesota School of Medicine, Veterans Administration Hospital, Minneapolis "Evaluation of the Factors Influencing the Discriminative Power of a Battery of Liver Function Tests" $8,250

Lewey, F.H., University of Pennsylvania Graduate School of Medicine, "Early and Late Phases of Peripheral Nerve Injuries" $21,400

Grundfest, H., Columbia University and Neurological Institute, "Investigation of Electromyographic, Autonomic, Vascular and Sensory Changes in Peripheral Nerve Injuries" $28,000

Shank, R.E., Washington University School of Medicine, St. Louis, MO, "A Cytochemical Study of Liver in Patients with Hepatic Disease with Particular Reference to the Metabolism of Carbohydrate and Nucleic Acid" $14,100

Lindsay, J.R., University of Chicago, "The Study of Functional and Histological Changes Resulting from Experimental Lesions of the Labyrinth" $8,892

Vandegrift, W.B., Veterans Hospital, Fort Howard, MD, "New Techniques in Preparation of Tissue for Microscopic Examination" $3,000

Wisenbaugh, P.E., Veterans Administration Hospital, Cleveland, OH, "Effects of Selective Depletion of Plasma Albumin in Dogs" $3,300

Smith, W.K., University of Rochester, School of Medicine, Rochester, NY, "Functions Represented in the Medial and Basal Regions of Cerebral Cortex. Normal Responses and Effects of Lesions" $7,300

Kobrak, H.G., University of Chicago, Chicago, "A Systematic Study on the Utilization of Prosthetic Appliances in the Middle Ear for Treatment of Conduction Type Deafness" $3,950

Thomas, C.B., Johns Hopkins Medical School, Baltimore, MD, "Study of Precursors of Hypertenson and Coronary Artery Disease" $20,500

Peters, H.N., VA Hospital, North Little Rock, AK, "Habit Retraining During Sub-shock Insulin Treatment in Schizophrenics" $31,305

Tarlov, I.M., New York Medical College, NY, NY, "Spinal Cord Compression: Experimental Study Bearing on Clinical Treatment" $7,500

1950 applications not approved: 40, including 12 with VA participation.

1951

Auerbach, S.H., Thayer VA Hospital, Nashville, TN, "Systematic Histologic Study of the Trachea and Bronchi" $2,925

Kingsley, G.R., Wadsworth VA Hospital, Los Angeles, CA, "A Study of the Relationship of Arsenic to Proteins and Other Components of Human Tumor Tissue" $9,100

Freeman, L.H., Indiana University Medical Center, Indianapolis, Indiana, "Possibility of Repair of the Injured Spinal Cord" $10,170 Renewal 1953 $16,000

Dochez, A.R., Veterans Administration Hospital, Bronx, N.Y., "Immunochemical Studies on Rheumatoid Arthritis" $10,750

Lucke, B., Armed Forces Institute of Pathology, Washington, DC, "Diagnosis of Neoplasia" $5,000

Grady, H.G., Armed Forces Institute of Pathology, Washington, DC, "Study of Pathology of Disease in Military and Veterans Age Group. Production of Educational Material in this Field" $20,000

Crocker, T.T., University of California Medical School, San Francisco, CA, "Chemical and Metabolic Studies of the Virus of Meningo-Pneumonitis" $17,715

Grino, A., Cleveland VA Hospital Cleveland, OH, "Regeneration of the Central Nervous System" $3,700

Light, R.A., Vanderbilt University School of Medicine, Nashville, TN, "Role of the Autonomic Nervous System in Control of the Pulmonary Vascular Bed" $9,950

Salkin, D., Weimer, H.E., Boak, R.A., V.A. Hospital, San Fernando, CA, "Distribution of Serum Polysaccharides in Tuberculosis" $4,550

1951 applications not approved: 22, including 8 with VA participation.

1952

Yeoman, A., VA Hospital, White River Junction, VT, "Clinical Chemical Studies of Acid-Base Abnormalities" $7,400

Howry, D. H., VA Hospital, Denver, CO, "The Utilization of Ultra High Frequency Sound for the Visualization of Soft Tissue Anatomy and Pathology" $27,468

Rosvold, H.E., Yale University School of Medicine, Department of Psychiatry, New Haven, CT, "The Psychobiology of Emotional Behavior" $22,000 Renewal 1953 $15,000

Blades, B., George Washington University, Washington, DC, "Effect of Lung Ischemia Upon Pulmonary Function." $9,439

Beecher, H.K., Massachusetts General Hospital, "Study of Metabolic & Other Latent Effects of Hypotensive Spinal Anesthesia" $10,400

Campbell, J.B., Columbia University, NY, "Use of Sterotaxically Placed Radon for Selected Quantitated Lesions in the CNS of Laboratory Animals" $5,101 Renewal 1953 $11,749

1952 applications not approved: 13, including 5 with VA participation.

1953

Washer, F.E., National Bureau of Standards, Washington, D.C., "Development of Performance Specifications for corrected Curve Lenses" $8,125

Blades, B, George Washington University Hospital, Washington, D.C., "Studies in Liver Circulation" $9,978

Freeman, L.H., Indiana University Medical Center, “Possibility of Repair of the Injured Spinal Cord” $16,000

Crocker, T.T., University of California Medical School, San Francisco, CA, “Chemical and Metabolic Studies of the Virus of Meningo-Pneumonitis” $17,715

Light, R.A., Vanderbilt University School of Medicine, Nashville, TN, “Role of the Autonomic Nervous system in Control of the Pulmonary Vascular Bed” $9,300

Washer, F.E., National Bureau of Standards, Washington, DC, “Development of Performance Specifications for ‘Corrected Curve’ Lenses” $8,125

Harvey, A. M., The Johns Hopkins Hospital, Baltimore, MD, “Application of Stable Isotopes to Medical Problems of Research and Practice” $9,500

Doull, J.A., Leonard Wood Memorial, Washington, DC, “Clinical Evaluation Studies in Leprosy” $3,000

Pincus, G., Hoagland, H., The Worcester Foundation for Experimental Biology, Shrewsbury, MA, “Assessment of the Functional Status of the Adrenal Cortex and Gonads by Urinary Steroid Analysis in Psychotic and Non-Psychotic Subjects” $15,300

Shambaugh, G., Jr., and Carhart, R., Northwestern University, “Evaluation of the Supplemental Value of the Aquaphor Prosthesis for the Post-Fenestrated Ear” $4,850

Urist, M.R., University of California Los Angeles School of Medicine, “The Mechanism of Osteogenesis in Normal and Slow Healing Fractures, Delayed and Non-Union, Bone Defects from War Wounds, and Various Bone Graft Operations” $15,000

Kobrak, H. G., “Artificial Sound Conduction in the Ear. A Clinical and Laboratory Investigation on the Improvement of Sound Conduction in The Ear by Usage of Middle Ear Prosthesis” $1,000

1953 applications not approved: 18, one of them with VA participation.

(Intentionally Blank)

Appendix IVb. Contracts for Research in Prosthetics and Sensory Aids begun before 1950

Contractor	Approx dates	Important contributions
Haskins Laboratories New York	1944–1954	Tested sensory devices for Committee on Sensory Aids
Northrop Aircraft Hawthorne, CA (Birmingham VA, Van Nuys, CA)	1945–1951	Requirements for arm prosthesis Shoulder-shrug operated elbow Improved hook control Wrist rotation for below elbow arms Suction socket, light-weight prostheses
UC Berkeley	1945–1970s	Fundamental studies on human locomotion Improved analysis of limb alignment Improved socket design Four-bar linkage knee Six-bar knee for knee disarticulation amputees
Northwestern Univ.	1945–1954	Literature and patent review Evaluation of newly developed artificial limbs
Alderson Research (originally IBM)	1946–1952	Electric arm development and evaluation
Catranis, Inc Syracuse, NY	1946–1950	Foot, knee, integrated leg development
UCLA	1946–1970s	Fundamental studies on arm and hand motion Clinic started 1952 – trained prosthetists
New York University	1948–1970s	Evaluation of artificial limbs
Mauch Laboratories Dayton, OH	1948–1978	Swing-and-stance hydraulic control knee Hydraulic ankle Reading machines

(Intentionally Blank)

Appendix Va. Radioisotope Services active in September, 1962[1]

Hospitals with full licenses (clinical and research)

Albany, New York	Charles A. Hall, M.D.
Albuquerque, New Mexico	G. A. Youngman, M.D.
Ann Arbor, Michigan	James Sisson, M.D.
Atlanta, Georgia	James C. Coberly, M.D.
Birmingham, Alabama	James A. Pittman. Jr., M.D.
Boston, Massachusetts	Belton A. Burrows, M.D.
Bronx, New York	Solomon A. Berson, M.D.
Brooklyn, New York	vacant
Buffalo, New York	Richard P. Spencer, M.D.
Chicago Research, Illinois	John A. D. Cooper, M.D.
Chicago Westside, Illinois	G. A. Williams, M.D.
Cincinnati, Ohio	John Imarisio, M.D.
Cleveland, Ohio	Reginald A. Shipley, M.D.
Coral Cables (Miami), Florida	C. G. Wherry, M.D.
Dallas, Texas	J. R. Rubini, M.D.
Dearborn, Michigan	E. R. Powner, M.D.
Denver, Colorado	H. Elrick, M.D.
Durham, North Carolina	M. P. Liebling, M.D.
East Orange, New Jersey	Maurice Small, M.D.
Fort Howard, Maryland	A. T. Faulk, M.D.
Fresno, California	S. H. Cheu, M.D.
Hines, Illinois	Ervin Kaplan, M.D.
Houston, Texas	Clarence P. Alfrey, M.D.
Indianapolis, Indiana	Leo Oliner, M.D.
Iowa City, Iowa	Richard E. Peterson, M.D.
Jackson, Mississippi	Arthur T. Tuma, M.D.
Kansas City, Kansas	Paul R. Schloerb, M.D.
Little Rock, Arkansas	H.H. Perkins, M.D.
Long Beach, California	Ralph E. Bodfish, M.D.
Los Angeles, California	William H. Blahd, M.D.
Louisville, Kentucky	N. Nataro, M.D.
Madison, Wisconsin	Frank Larson, M.D.
Martinsburg, West Virginia	Arthur F. Abt, M.D.
Memphis, Tennessee	M.L. Fields, M.D.
Minneapolis, Minnesota	Leslie Zieve, M.D.
Nashville, Tennessee	W.L. Alsobrook, M.D.
New Orleans, Louisiana	E.H. Bresler, M.D.
New York, New York	Marcus A. Rothschild, M.D.
Oakland, California	Jack F. Mangum, M.D.
Oklahoma City, Oklahoma	Walter H. Whitcomb, M.D.
Omaha, Nebraska	Richard E. Ogborn, M.D.
Philadelphia, Pennsylvania	Arlyne T. Shockman, M.D.
Pittsburgh (Univ Dr), Pennsylvania	John Vester, M.D.

Portland, Oregon	John R. Walsh, M.D.
Providence, Rhode Island	B.C. Claunch, M.D.
Salt Lake City, Utah	Lindy Kumagai, M.D.
San Francisco, California	vacant
San Juan, Puerto Rico	J.V. Rivera, M.D.
Seattle, Washington	Clayton Rich, M.D.
St. Louis, Missouri	Neil I. Gallagher, M.D.
Syracuse, New York	Robert B. Chodos, M.D.
Washington, D.C.	William McFarland, M.D.
West Haven, Connecticut	D.L. Buchanan, M.D.
Wood, Wisconsin	Robert C. Meade, M.D.

Hospitals with limited licenses

Augusta, Georgia
Baltimore, Maryland
Batavia, New York
Bay Pines, Florida
Big Spring, Texas
Dayton, Ohio
Des Moines, Iowa
Fort Harrison, Montana
Grand Junction, Colorado
Huntington, West Virginia
Kecoughtan, Virginia
Oteen (Asheville), North Carolina
Perry Point, Maryland
Pittsburgh (Leach Farm Road), Pennsylvania
Richmond, Virginia
Sepulveda, California
Sunmount, New York
Togus, Maine
Tucson, Arizona
Wadsworth, Kansas
West Roxbury, Massachusetts
White River Junction, Vermont

1. "Research in radioisotopes: Veterans Administration radioisotope services." *Research and Education Newsletter*, December, 1962. 16.

Appendix Vb. Clinical uses of radioisotopes in VA hospitals, FY 1962[1]

(65 hospitals)

Diagnostic Uses	Patients	Tests
Evaluation of Thyroid Status (1-131)	11,744	14,893
Thyroid Scans (1-131)	1,761	1,868
Protein-bound iodine (1-131)	723	764
Tri-iodo-thyronine binding (in-vitro)	878	2,294
Blood volume (1-131 HSA)	3,071	3,526
Red cell mass, survival time, or GI loss (Cr-51)	2,511	3,490
Schilling test (Co-60, Co-58, or Co-57)	2,153	2,935
Ferro-kinetics (Fe-59)	327	374
Coronary flow or radiocardiogram	517	634
Fat absorption Studies (1-131)	1,477	1,950
Kidney function or renograms (Hippuran, etc.)	2,283	2,668
Liver Function (1-131 Rose Bengal)	401	423
Electrolyte balance measurements (K-42, Na-24, etc.)	347	367
Brain Tumor localization	139	143
Miscellaneous	802	862
Total	29,134	37,191

Therapeutic Uses	Patients	Doses
Hyperthyroidism (1-131)	426	521
Thyroid ablation in Cardiac disease (1-131)	35	66
Thyroid Carcinoma (1-131)	19	20
Polycythemia vera or leukemia (P-32)	164	284
Malignant effusion (Au-198 or $CrP0_4$)	26	26
Bone Metastases (P-32 Polymetaphosphate)	20	44
Miscellaneous	8	8
Total	698	969

1. Moseley, A. Graham, "Consolidated report of clinical uses of radioisotopes." *Research and Education Newsletter,* September, 1962. 17.

(Intentionally Blank)

Appendix VI. Special Laboratories Active During the 1950s and 1960s

Oncology

Cancer and Leukemia	Ludwig Gross (Became Senior Medical Investigator in 1958)	Bronx	1953-58
Cancer Research	Leslie Zieve	Minneapolis	1961-68

Gastroenterology

Gastrointestinal Research	David Sun,	Wash, D.C.	1961-66
Liver and Metabolic Research	Hyman Zimmerman	Wash, D.C.	1965-68

Neuropsychiatry

Epilepsy, later called Neurology	F.A. Quadfasel	Boston	1952-62
Neurophysiology-Biophysics Research	Robert Efron (Became Medical Investigator in 1971)	Boston	1961-71
Neuropharmocology	Amadeo Marrazzi	Pittsburgh	195?-56
Psychopharmacology	William Clark	Sepulveda	1960-69
Psychiatric and Psychosomatic Res.	Roy Mefferd	Houston	1958-68
Study of Unpredicted Deaths	Edwin S. Schneidman later Norman Farberow	Wadsworth	1958-70

Special Dental Laboratories

Dental Prostheses for Elderly	unknown PI	Bay Pines	195?-57
Dental Filling Materials	unknown PI	Long Beach	195?-57
Development of Dental Structures	unknown PI	Coral Gables	195?-56
Oral Tissue Metabolism	Philip Person (Became Medical Investigator in 1970)	Brooklyn	1955-70
Oral Physiology	Ira Shannon	Houston	1967-70

Tuberculosis, infectious and pulmonary diseases

Tuberculosis	Martin Cummings until 1953, then unknown PI	Atlanta	1950-57
Tuberculosis	unknown PI	Baltimore	195?-57
Pulmonary Diseases	Lloyd Hedgecock	Kansas City	19??-61
New Tuberculosis Drugs	unknown PI	West Haven	195?-56
Tuberculosis	Edwin Brosbe	Long Beach	195?-61
Mycobacteria	Ernest Runyon	Salt Lake City	1958-63
Microbiology	Stuart Mudd	Philadelphia	1959-68
Chronic Infectious Disease	Gladys Hobby	East Orange	1960-8

Other

Medical Electronic Data Processing,	Hubert Pipberger, (Became Medical Investigator in 1971)	Wash, D.C.	1957-71
Pituitary Bank	Harold Elrick	Denver	1959-63
Domiciliary Lipid Diet Research	Seymour Dayton	Wadsworth and Phoenix	1959-70

Normative Aging Study	Benjamin Bell later Jeremiah Silbert, then Pantel Vokonas	Boston OPC	1963-present
Nuclear Medicine and Biology	Merton Quaife	Omaha	1964-67

Special Laboratories in Support of Cooperative Studies

Central Neuropsychiatric Research Lab	Quentin Holzapple then James Klett	Perry Point (Ch. 8)	1958-75
Outpatient Psychiatry Research	Maurice Lorr	Washington, D.C. (Ch.8)	1953-67
Tuberculosis Coop Study Control Lab	William Redmond later Ruth Wichelhausen	Atlanta	1958-68

Appendix VII. Publications from VA Research Service in the 1950s and 1960s

Periodicals

Medical Research in the Veterans Administration, the annual report to Congress. Published annually, 1957 through 1975:

R&E Newsletter, Research and Education in Medicine. Published several times a year, 1960 through 1968.

VA medical monographs reporting work by the Follow-up Agency:

(1) *Tuberculosis in the Army of the United States in War II*, 1955.
(2) *A Follow-Up Study of World War II Prisoners of War*, 1955.
(3) *A Follow-Up Study of War Neuroses*, 1956.
(4) *Peripheral Nerve Regeneration: A Follow-Up Study of 3,656 World War II Injuries*, 1957.
(5) *A Follow-Up Study of Head Wounds in World War II*, 1961.

Other

VA Prospectus, Research in Aging, 1958
Thyroid Scanning, a manual, 1960
The Interim Report of the VA Cooperative Study on Oral Exfoliative Cytology, 1961

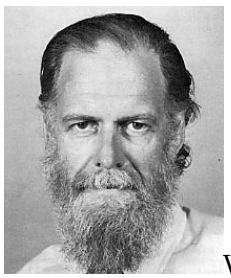
(Intentionally Blank)

Appendix VIII. Research Career Scientists appointed before 1981

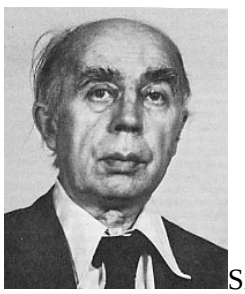
1978

Khahlil Ahmed, Ph.D. Minneapolis	Toxicology

Virginia E. Davis, Ph.D. Houston	Cellular mechanisms of tolerance of and dependence on alcohol and related drugs



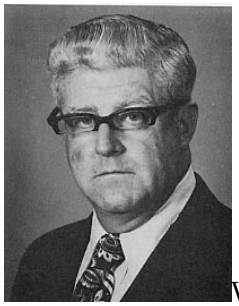
Walter B. Dempsey, Ph.D. Dallas	Medical and microbial genetics



Silvio Fiala, M.D. Martinsburg	Chemical carcinogenesis

Harvey F. Fisher, Ph.D. Kansas City — Molecular biochemistry

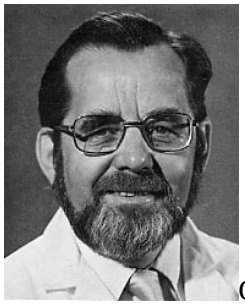
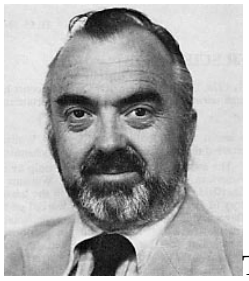
James M. Fujimoto, Ph.D. Wood — Pharmacology of addicting drugs



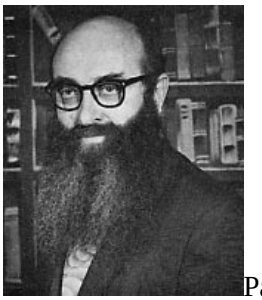
William R. Goff, Ph.D. West Haven — Neurophysiology

G.D. Hsiung, Ph.D. West Haven — Virology

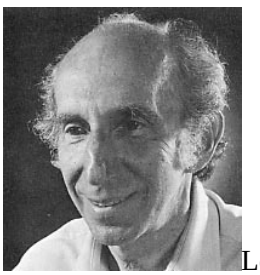
Milton Huppert, Ph.D. Long Beach — Medical mycology

 George Melnykovych, Ph.D.	Kansas City	Cell biology and cancer research
 Carlo Moscovici, Ph.D.	Gainesville	Genetics and biology of oncoviruses
 Thomas B. Mulholland, Ph.D.	Bedford	Psychophysiology
 Herbert T. Nagasawa, Ph.D.	Minneapolis	Medicinal chemistry

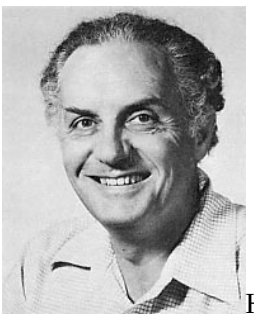
Martin Sax, Ph.D. Pitsburgh UD — X-ray crystallography of proteins



Paul A. Srere, Ph.D. Dallas — Cellular enzymology



Leo Vroman, Ph.D. Brooklyn — Physiology of interfaces

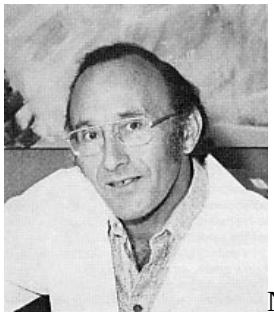


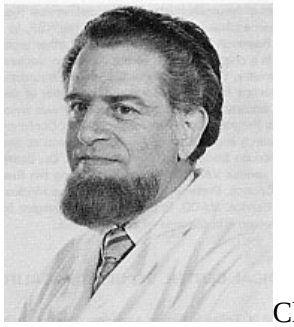
Harry Walter, Ph.D. Long Beach — Biology of cell surfaces


Charles H. Williams, Jr., Ph.D. Ann Arbor Enzyme biochemistry


Joseph Zubin, Ph.D. Pittsburgh HD Evaluation of psychiatric treatments

1979


Nome Baker, Ph.D. LA (Wadsworth) Tumor-lipid biochemistry

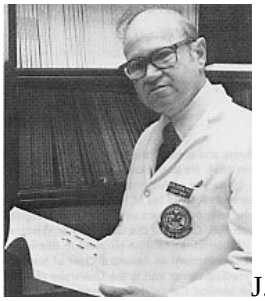

Claude F. Baxter, Ph.D. Sepulveda Neurochemistry


Denis R. Burger, Ph.D. Portland Histocompatability

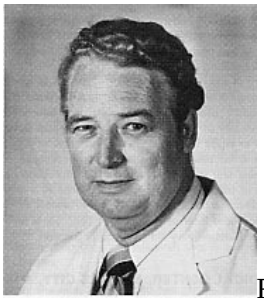

Daniel G. Colley, Ph.D. Nashville Infectious diseases


Allen Frazer, Ph.D. Philadelphia Biology of psychiatric disorders

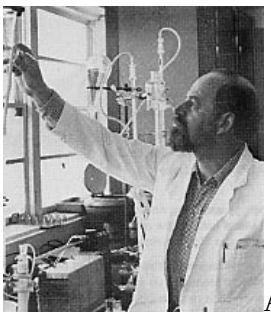

James W. Hamilton, Ph.D. Kansas City Hormone biochemistry



J. Alan Johnson, Ph.D. Columbia, MO — Genesis of hypertension



Raymond Lindsay, Ph.D. Birmingham — Physiology and pharmacology of thyroid



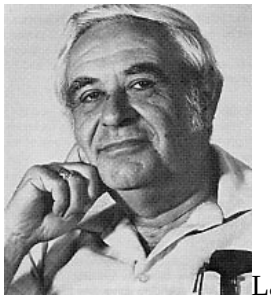
Alfred Linker, Ph.D. Salt Lake City — Connective tissue polysaccharides

Richard N. Lolly Sepulveda — Neuropathology, especially of the retina

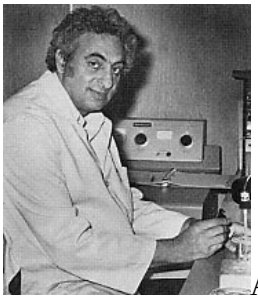
Vladimir Pushkin, Ph.D. Oklahoma City Neuropsychology

Michael Schotz, Ph.D. LA(Wadsworth) Lipid and lipoprotein biochemistry

Kosaku Uyeda, Ph.D. Dallas Enzyme biochemistry



Lawrence G. Wayne, Ph.D. Long Beach Bacteriology

 Arthur Yuwiler, Ph.D. LA (Brentwood) Neurobiochemistry

1980

 Truett Allison, Ph.D. West Haven Electrophysiology

 Joseph Bernsohn, Ph.D. Hines CNS metabolism

 Liard S. Cermak, Ph.D. Boston Memory

Donnell Creel, Ph.D. Salt Lake City — Anatomy and electrophysiology of vision

Thomas L. Feldbush, Ph.D. Iowa City — Immunologic memory

Robert J. Fitzgerald, Ph.D. Miami — Oral microbiology

Robert G. Garrison, Ph.D. Kansas City — Microbiology

	Charles C. Irving, Ph.D. Memphis	Chemical carcinogenesis
	Don Justesen, Ph.D. Kansas City	Behavioral and electrophysiological effects of microwave irradiation
	Margaret W. Linn, Ph.D. Miami	Stress and oncology
	Ulysses S. Seal, Ph.D. Minneapolis	Biochemical endocrinology

 M. Barry Sherman, Ph.D. Sepulveda Neuropsychology

 F. Thomas Shipp, Ph.D. San Francisco Speech pathology

Appendix IX. Alcoholism scholars, 1979-1983

Round 1 – started 3-year appointments in 1979. Recruited from outside of VA

Awardee	Sponsoring VAMC	Research topic	Current status 2002
Bertram I. Cohen, Ph.D.	New York, NY	Effects of alcohol on lipid metabolism in experimental animals and man	In NYU- affiliated hosp, studying lipids
John C. Crabbe, Ph.D.	Portland, OR	Systematic analysis ofthe relationships among several responses to ethanol using a behavior/ genetic approach	Alcohol research Portland VAMC
Edward Gallaher, Ph.D.	Palo Alto, CA	A physiological approach to the study of ethanol tolerance and physical dependence: The application of control system analysis	Alcohol research Portland VAMC
R. Adron Harris, Ph.D.	Columbia, MO	Effects of alcohol intoxication and dependence on ion transport and neurotransmitter release by synaptosomes	Alcohol research University of Texas
Anastascio Hoyumpa, M.D.	Nashville, TN	Alcohol and thiamine metabolism	Alc.&liver research San Antonio VAMC
William Kenney, Ph.D.	San Fran, CA	Influence of ethanol and acetaldehyde on membrane-bound enzymes	Retired from Amgen
Elizabeth Rowe, Ph.D.	Kansas City, MO	Molecular mechanisms of alcoholism	Alc.&lipid research Kansas City VAMC
Marc Schuckit, M.D.	San Diego, CA	A basic research program to study etiology of alcoholism	Alcohol research San Diego VAMC
Francis R. Simon, M.D.	Denver, CO	Effect of alcohol ingestion on the structure and function of liver surface membrane	Alc&liver research Denver VAMC

Boris Tabakoff, Ph.D	Chicago WS, IL	Dopamine and neurohypophyseal peptides in alcohol tolerance&depend'ce	Alcohol research Univ Colorado High positions in NIAAA 1984-1990
Anna N. Taylor, Ph.D.	Brentwood, CA	Fetal alcoholism in rats: Central neural effects; an animal model for addiction	Alcohol research West LA VAMC
Pushpa Thadani, Ph.D.	Washington, DC	Effects of acute and chronic maternal ethanol ingestion on maturation of CNS, endocrine and cardiovascular systems in the offspring	Leads neuroscience center at NIDA
Ladislav Volicer, M.D., Ph.D.	Boston, MA	Study of etiol. of alcoholism and the investigation of the biochemical- pharmacologic and cellular biologic effects and responses to alcohol	Dementia research Bedford VAMC

Round 2 – started 3 year appointments in 1980. Both VA and non-VA investigators eligible

Awardee	Sponsoring VAMC	Research topic	Current status 2002
Enrique Baraona, M.D.	Bronx, NY	Mechanism and consequence of the alcohol-induced alterations of microtubules	Alcohol research Bronx VAMC (retired)
M. Raj Lakshman, Ph.D.	Washington, DC	Metabolic and genetic basis for alcoholic hyperlipidemia	Alcohol research Washington VAMC
Lawrence Lumeng, M.D.	Indianapolis IN	Genetic and biochemical factors in the etiology of alcoholism	Alcohol research Indianapolis VAMC
Carrie L. Randall, Ph.D.	Charleston, SC	Offspring of alcoholics: An animal model to study the etiology of alcoholism	Alcohol research Medical Univ. SC
Thomas L. Smith, Ph.D.	Tucson, AZ	Neurochemical prerequisites of alcohol addiction	Alcohol research Tucson VAMC

M. David Ullman, Ph.D.	Bedford, MA	Contribution of structural lipids to the etiology of alcoholism	Geriatrics&alc. res Bedford VAMC

(Intentionally Blank)

Appendix X. Persons interviewed

William Adams, M.D.
Ernest Allen, Ph.D.
Herbert Allen, M.D.
Hal O. Anger
Joan Armer, R.N.
Oscar Auerbach, M.D.
Clifford Bachrach, M.D.
John Bailar, M.D.
Maureen S. Baltay
Marion Barry
Claude Baxter, Ph.D.
Chester Bazel, R.Ph.
Gilbert Beebe, Ph.D.
Howard Berman
Leon Bernstein, M.D.
Lionel Bernstein, M.D.
William Best, M.D.
Robert Birch, M.D.
William Blahd, M.D.
Dorothy Bluestein
Hollis Boren, M.D.
Linda Boxer, M.D., Ph.D.
Marion Brault
Norman Q. Brill, M.D.
Ernest Burgess, M.D.
Belton Burrows, M.D.
Allen B. Cady, M.D.
Eugene Caffey, M.D.
Arthur Cain, M.D.
Chu Carr
Jules Cass, D.V.M.
Ralph Casteel
Thomas Chalmers, M.D.
Sonny Chang, Ph.D.
John D. Chase, M.D.
Robert A. Chase, M.D.
Howard H. Chauncey, Ph.D., D.M.D.
Lawrence G. Christianson, M.D.
Sidney E. Cleveland, Ph.D.
Betty Cobbs
Marvin Cohen, M.D.
David Cohn, Ph.D.
Frank Coombs
John A.D. Cooper, M.D.

Gregory Crowe
Lawrence Crowley, M.D.
Martin Cummings, M.D.
David N. Daniels, M.D.
Carolyn Davidson
Kenneth Davis, M.D.
Michael DeBakey, M.D.
Chester DeLong, Ph.D.
Walter Dempsey, Ph.D.
Gerald DeNardo, M.D.
Paul Densen, Ph.D.
Nicholas D'Esopo, M.D.
Vincent DeVita, M.D.
Daniel Deykin, M.D.
Harold (Jack) Divers
Abraham Dury, Ph.D.
Richard V. Ebert, M.D.
E.E. Eddleman, M.D.
Robert Efron, M.D.
Roger Egeberg, M.D.
Seymour Eisenberg, M.D.
Frederick Eldridge, M.D.
James Elliott, M.D.
Robert Ellsworth, Ph.D.
Lawrence Eng, Ph.D.
H. Martin Engel, M.D.
Carleton Evans, M.D.
George Fairweather, Ph.D.
Robert Farese, M.D.
Lori Fertel
William Figueroa, M.D.
Richard Filer, Ph.D.
James Finklestein, M.D.
Robert Fitzgerald, Ph.D.
Robert Fleming
Lysia Forno, M.D.
Irene Forrest, Ph.D.
William H. Forrest, M.D.
Laurence Foye, M.D.
James Fozard, Ph.D.
Earl Freed, Ph.D.
Edward Freis, M.D.
Andrew Gage, M.D.
Al Gavazzi
Samuel Gershon, M.D.
Bruno Gerstl, M.D.

Margaret Giannini, M.D.
Gerald Goldstein, Ph.D.
Richard Goode, M.D.
Harold Goodglass, Ph.D.
Clo Gooding
Gregory Goodrich, Ph.D.
David Goodwin, M.D.
Earl Gordon, M.D.
Abraham Gottlieb, M.D.
Mark Graeber, M.D.
Howard W. Green, M.D.
Richard Greene, M.D., Ph.D.
Ludwig Gross, M.D.
George Gulevich, M.D.
Lee Gurel, Ph.D.
Paul Haber, M.D.
Francis Haddy, M.D., Ph.D.
James Hagans, M.D., Ph.D.
Charles Hall, M.D.
Charles H. Halsted, M.D., son of James Halsted, M.D.
Paul Heller, M.D.
Victor Herbert, M.D.
George Higgins, M.D.
Richardson Hill, M.D.
Gladys L. Hobby, Ph.D.
Esther Hodges
William Hofman, M.D.
Leo Hollister, M.D.
David S. Howell, M.D.
Herbert N. Hultgren, M.D.
Seymour Jablon
Henry Jones, M.D.
Samuel C. Kaim, M.D.
Martin S. Kalser, M.D., Ph.D.
Eugene Kanabrocki, Ph.D.
Ervin Kaplan, M.D.
Abba Kastin, M.D.
Laurence H. Kedes, M.D.
Paul Kennedy
Robert Kevan
C. James Klett, Ph.D.
Leonard Knott
Shoichi Kohatsu, M.D.
Bert Kopell, M.D.
Ross Kory, M.D.
Jon C. Kosek, M.D.

Leonard Krasner, Ph.D.
Jeannette Landis
Milton Landowne, M.D.
Alfred Lawton, M.D.
Lyndon Lee, M.D.
Larry Leifer, Ph.D.
Gerald Libman
Charles Lieber, M.D.
Clyde J. Lindley
Armand Littman, M.D.
Richard Lolley, Ph.D.
Leon Lombroso, Ph.D.
Theodore Lorei, M.S.W.
Maurice Lorr, Ph.D.
Sanford Mabel, Ph.D.
Roy Maffley, M.D.
Joseph Mason
Jack Matoole, M.D.
James H. Matthews, M.D.
Richard Mazze, M.D.
Willa McBride
Donna McCartney
Burley McCraw
Dennis McGinty, Ph.D.
Paul W. McReynolds, Ph.D.
Jeffrey Meade, M.D., son of Robert Meade, M.D.
Shirley Meehan, Ph.D., M.B.A.
Sherman Mellinkoff, M.D.
Thomas Merigan, M.D.
Joe Meyer, Ph.D.
Ralph Meyerson, M.D.
James Grier Miller, M.D., Ph.D.
Anne Moore
Rudolph Moos, Ph.D.
James Moses, Ph.D.
Eugene F. Murphy, Ph.D.
Wendell Musser, M.D.
Boyce Nall
Thomas Newcomb, M.D.
Vernon Nickel, M.D.
John C. Nunemaker, M.D.
Charles P. O'Brien, M.D., Ph.D.
William H. Oldendorf, M.D.
John Overall, Ph.D.
William Page, Ph.D.
William Pare, Ph.D.

Cecil Peck, Ph.D.
Inder Perkash, M.D.
John Peters
Jon Peters, P.T.
Adolph Pfefferbaum, M.D.
Lajos Piko, Ph.D.
James A. Pittman, M.D.
Robert Prien, Ph.D.
John Prusmak, M.D.
Jose Rabinowitz, Ph.D.
Malcolm J. Randall
Gerald Reaven, M.D.
Paul Rogers, Esq.
Charles A. Rosenberg, M.D.
Joseph Ross, M.D.
Bernard Roswit, M.D.
Dennis Roth
Walton Thomas Roth, M.D.
Marcus Rothschild, M.D.
Robert Rynearson
Mohinder Sambhi, M.D.
Andrew Schally, Ph.D.
Harold Schnaper, M.D.
Robert Schneiter
Harold Schoolman, M.D.
Robert Schrek, M.D.
Ruth Schrek
Leonard Seeff, M.D., Ch.B.
Robert Shamaskin
Lawrence Shaw
Austin Shug, Ph.D.
Jay Shurley, M.D.
David G. Simons, M.D.
Orin T. Skouge, M.D.
James J. Smith, M.D.
Marion Smith, Ph.D.
David H. Solomon, M.D.
George F. Solomon, M.D.
Harold Sox, M.D.
Herta Spencer, M.D.
Jerry Spenney, M.D.
Leonard Spolter, Ph.D.
Norton Spritz, M.D.
Paul Srere, Ph.D.
Barry Sterman, Ph.D.
Robert E. Stewart, D.D.S.

Richard Streiff, M.D.
Leon Swell, Ph.D.
Robert Swenson, M.D.
Keith Taylor, M.D.
David D. Thomas
William C. Thomas, M.D.
Samuel Threefoot, M.D.
Jereld R. Tinklenberg, M.D.
Leonard Ullman, Ph.D.
Roger H. Unger, M.D.
Kosaku Uyeda, Ph.D.
William Valentine, M.D.
Hugh Vickerstaff
Harry E. Walkup, M.D.
John Weakland
James Wear, Ph.D.
Fred Weibell, Ph.D.
Louis Jolyon West, M.D.
Walter Whicomb, M.D.
Darlene Whorley
Clyde Williams, M.D., Ph.D.
John Willoughby
Marjorie T. Wilson, M.D.
Mark Walcott, M.D.
Julius Wolf, M.D.
Stewart G. Wolf, M.D.
Rosalyn S. Yalow, Ph.D.
Jerome Yesavage, M.D.
Larry Yuen
Vincent P. Zarcone, M.D.
Leslie Zieve, M.D.
Hyman Zimmerman, M.D.
Eugene Zukowsky, Ph.D.

Appendix XI. Organization of research within the VA

The VA research program reflects the nature of the VA itself, a service organization dedicated to the American war veteran. Research has always been an integral part of the VA, but the VA's structure has changed with time, as has the status of its research component. This description is intended to reduce confusion for the reader who is not familiar with this structure. The major changes with time are summarized as organizational charts.

The research unit has consistently been part of the VA's medical program, which itself is a part of a larger organization with additional responsibilities (pensions, insurance, etc). Until 1930, the overall organization was called the Veterans' Bureau (with narrower responsibilities). It then became the Veteran's Administration, with a broader charge. In 1989, Congress made it a Cabinet-level Department, the Department of Veterans Affairs. For simplicity, here the organization will usually be called simply "the VA". The entire VA is headed by a Presidential appointee, called the Director until 1930, the Administrator for Veterans' Affairs until 1989 and subsequently the Secretary for Veterans' Affairs.

The medical program was called the Medical Service until 1946, when a new law redefined it. It was then called the Department of Medicine and Surgery (DM&S) until 1989, and now it is the Veterans' Health Administration. Its leader was called the Medical Director from 1922 to 1946, the Chief Medical Director (CMD) from 1946 to 1989, and is now the Undersecretary for Health. He reports to the Administrator or Secretary.

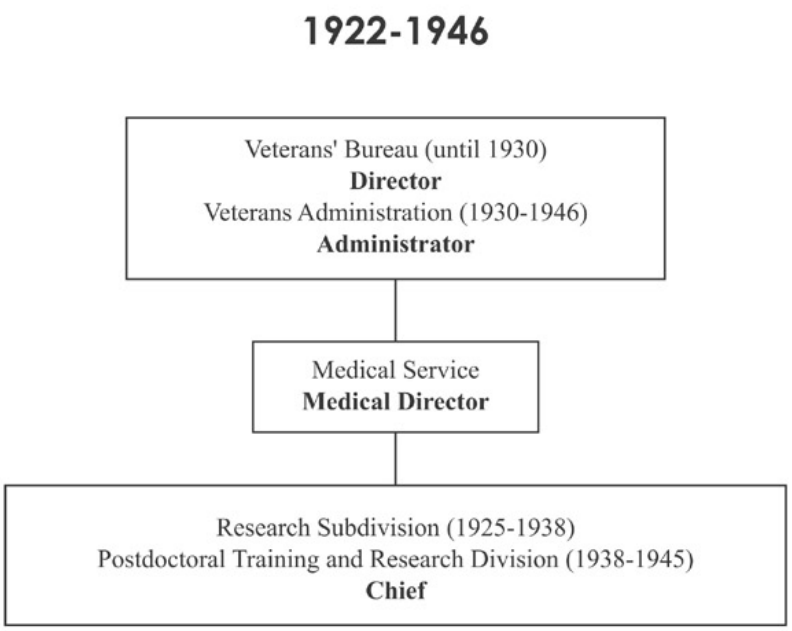


Figure AppXI.1: VA organization, 1922-1946

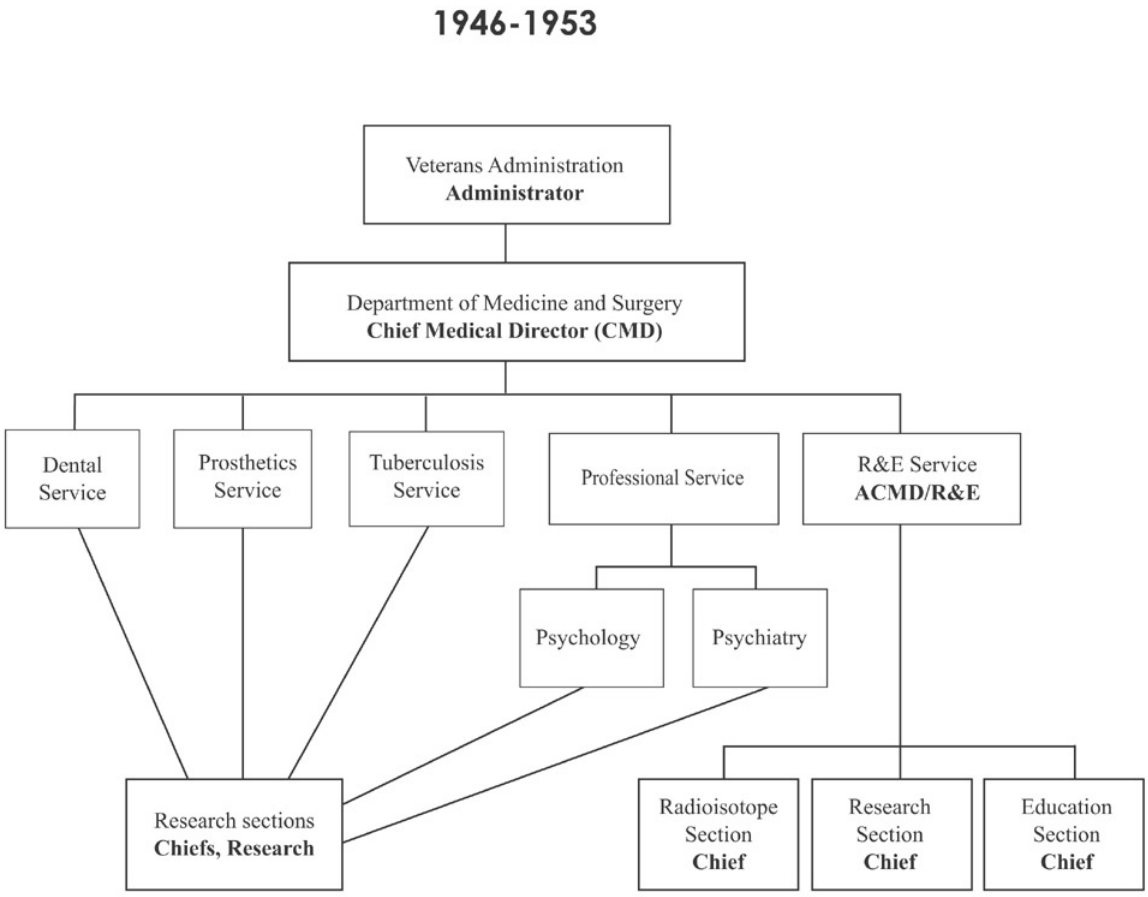


Figure AppXI.2: VA organization, 1946-1953

Most of the early research after the end of World War II was clinical in nature. In fact, some of the most important early research studies (the tuberculosis studies and the psychopharmacology studies) emanated from offices primarily responsible for direct patient care. As a separate Research Service grew within the Central Office, its members worked with staff of these patient-care services to assist them in the research that they had begun. As time went on, Research Service took more and more responsibility for those studies.

Soon after the end of World War II, Research Chiefs were included on the staffs of a number of Professional Service units (Figure AppXI.2). During the 1960s, when Research Service had Program Chiefs in various patient care areas, there was active exchange between the Research Service Program Chiefs and the Research Chiefs in the respective patient care services. As the research program became stronger and more diverse in the 1970s and 1980s, the need for these formally designated Research Chiefs elsewhere in VACO decreased; but members of the patient care services continued to play an active advisory role in the research program.

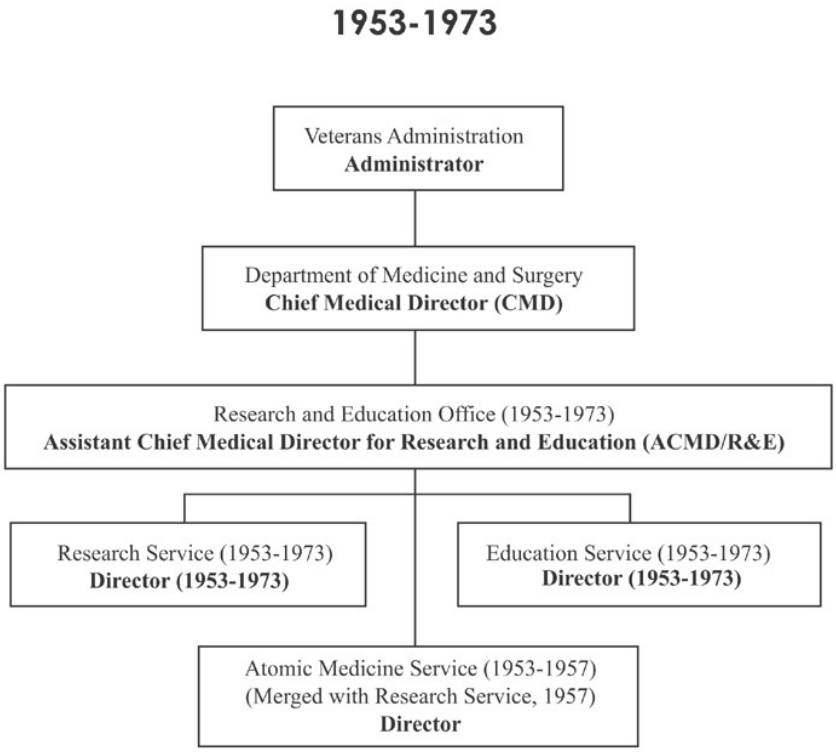


Figure AppXI.3: VA organization, 1953-1973

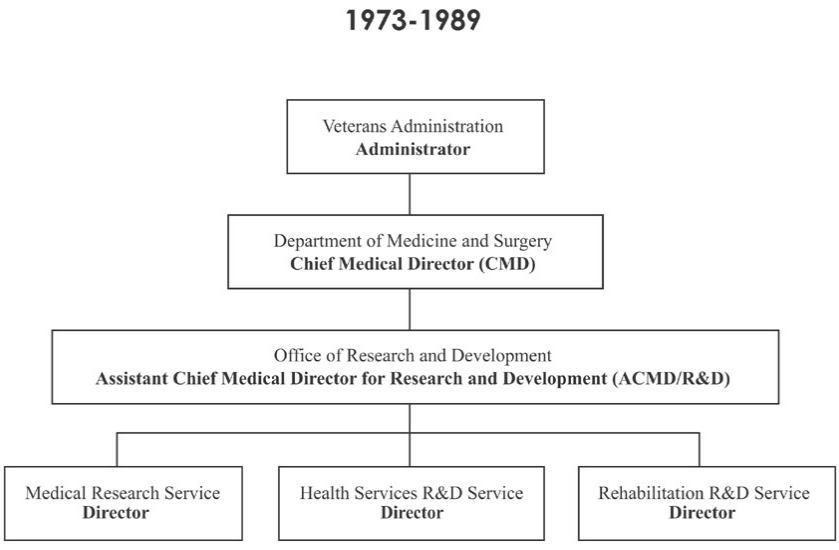


Figure App XI.4: VA organization, 1973-1989

(Intentionally Blank)

A

B

C

D

H

I

J

K

L

M

N

Q

R

S

T

U

V

W

Y

Z

For more than 85 years, the United States Department of Veterans Affairs (VA) Research and Development program has improved Veterans' lives through innovations and discoveries that have led to advances in health care for Veterans and all Americans. VA's Research program is the world's only research program focused wholly on conducting groundbreaking research to meet the full spectrum of Veterans' medical needs. The program takes full advantage of being part of an exceptional integrated health care system for Veterans, and of VA's state-of-the-art electronic health records system. Today's VA Research program is an acclaimed model for conducting superior bench-to-bedside research; attracts the best and brightest investigators, many of whom also work as VA clinicians; and quickly translates research findings into advancements in care and medical decision-making based on patient-centered evidence. While realizing the advantages of an intramural program and embracing its close affiliation with academic institutions, VA's Research and Development program fosters dynamic collaborations with federal agencies, private industry, and others—furthering the program's span of achievements and its national health impact.

Throughout its 85-year history, the first 55 years of which is documented in this book, VA research has established a superb record of discovery, innovation, and advancement that has benefited Veterans and all Americans. The history of VA research is a testimony to these achievements and the men and women who accomplished them, and also offers a glimpse at the Program's future.

Veterans Health Administration

R&D

www.research.va.gov

For questions or additional copies contact:
R&D Communications (12)
103 South Gay Street, Ste. 517
Baltimore, MD 21202
(410) 962-1800 x223
research.publications@va.gov

printed by GPO 2010

For more information, go to www.research.va.gov

Polytrauma
Hearing and Vision Loss
Posttraumatic Stress Disorder (PTSD)
Personalized Medicine
Access to Care
Cardiovascular Disease
Infectious Diseases
Prosthetics and Amputation Care
Pain Management
Substance Abuse
Post-Deployment Research
Traumatic Brain Injury
Kidney Disease
Mental Health
Spinal Cord Injury
Neurodegenerative Diseases
Women's Health
Diabetes