NOSOLOGICAL ENTITIES?

Reflex sympathetic dystrophy

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Does reflex sympathetic dystrophy (RSD) exist? If it does, how is it defined, what is its nature, and how is it treated? Reviewed on many occasions,[1–4] the subject engenders considerable and often heated debate. Some of the reasons for the continuing debate are summarised in this discussion.

The question of definition

HOW DID WE REACH THE PRESENT SITUATION?

In 1864 Silas Weir Mitchell, a founding father of American neurology, together with Morehouse and Keen, described the clinical condition of causalgia in soldiers injured in the American civil war.[5] This term, which means burning pain, was used to describe a particular painful condition that sometimes followed major nerve injury. The nerve injury, which was usually partial, typically affected a limb. The burning pain was often accompanied by additional features including various sensory disturbances; temperature and sweating changes; glossy and other disturbances of the skin, subcutaneous tissues, muscles and joints; paralysis; and involuntary movements.

Earlier this century, others noted that there were patients with a similar but less severe condition that resembled causalgia and again often followed trauma but without major nerve injury (although "major" has never been clarified). This condition has had many synonyms, including minor causalgia, post-traumatic vasomotor disorder, Sudeck's atrophy (a term which, strictly speaking, applies to the radiological appearance of osteoporosis), algodystrophy, and reflex sympathetic dystrophy. The last term was introduced in 1946 by Evans,[6] and is the one most commonly used today.

WHY REFLEX, WHY SYMPATHETIC, AND WHY DYSTROPHIC?

Evans envisaged that prolonged bombardment of pain impulses set up a "vicious circle of reflexes" in the spinal cord that generated efferent activity in the sympathetic system leading to spasm in the peripheral blood vessels. As a consequence there was leakage of fluid from the capillaries which eventually caused dystrophic changes in peripheral tissues.

The French surgeon Leriche had already noted that the limbs of patients with causalgia showed features that he thought reminiscent of vascular insufficiency. Because patients with ischaemic limbs were often treated by sympathectomy, Leriche argued by analogy that causalgia was due to an "irritation of the sympathetic" and might be alleviated by sympathectomy.[7] His views were apparently confirmed when a patient with causalgia was relieved of upper limb pain after Leriche had stripped 12 cm of adventitia from the brachial artery. These notions were later extended to RSD, although few noted that Leriche was later to retract his hypothesis.

FRUSTRATED ATTEMPTS AT DEFINITIONS

In recent years, attempts have been made to define the disorder(s) more satisfactorily. Unfortunately, these well intentioned aspirations have been rather unsuccessful.

In 1986, the International Association for the Study of Pain (IASP) defined RSD as "continuous pain in a portion of an extremity after trauma which may include fracture but does not involve a major nerve, associated with sympathetic hyperactivity". Eight years later IASP revised the nomenclature, introducing the new term "complex regional pain syndrome" (CRPS).[8] Type I CRPS is synonymous with RSD, and comprises "a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of oedema, changes in skin blood flow, abnormal sudomotor activity in the region of the pain, or allodynia or hyperalgesia." Type II CRPS is the term reserved for when the condition is associated with nerve injury—that is, causalgia.

The term CRPS is not widely known outside IASP circles, and although this revised nomenclature at least dispensed with the inclusion of the sympathetic nervous system, the definitions pose further questions, and yet another classification has recently been proposed in the journal *Pain*.[9] Various scoring systems have also been introduced to aid diagnosis, and sometimes researchers devise their own diagnostic criteria. Investigations do not disclose diagnostic abnormalities, and characterising RSD depends on clinical consensus derived from series of patients with any number of different features (even including absence of pain[6]) who are assessed at different stages of their illnesses. It is not surprising, therefore, that there are no universally accepted diagnostic criteria for this condition.

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Table 1 Various features that may accompany RSD and pain

Allodynia, hyperalgesia, hyperpathia, hyperaesthesia, dysaesthesia, hypoaesthesia
Skin erythematous, cyanosed, pale or blotchy
Excessive, reduced, or absent sweating
Inappropriate warmth or coldness
Swelling, atrophy, or pigmentation of skin
Loss of skin wrinkles or glossiness
Excess or loss of hair
Nails ridged, curved, thin, brittle, or clubbed
Subcutaneous atrophy or thickening
Dupuytren's and other contractures
Joint stiffness, acute or chronic arthritis
Osteoporosis: spotty, localised, or widespread
Muscle wasting and weakness
Involuntary movements: tremor, dystonia, spasms
Detrusor and urinary sphincter dysfunction

Modified from Schott[4] by permission of Oxford University Press.

Why is reflex sympathetic dystrophy difficult to characterise?

Two initial comments are pertinent. Firstly, many of the clinical features of RSD can be produced in healthy volunteers simply by immobilising a limb for a month.[10] Secondly, RSD can easily represent a "dustbin" diagnosis for any 'funny' pain in a 'funny-looking' limb"; and neurological disease such as peripheral neuropathy, but particularly various musculoskeletal disorders, may be misdiagnosed as RSD (see Schott[4]). However, characterising RSD is difficult for the reasons that follow.

VARIETY OF THE CLINICAL FEATURES

One of the most important difficulties is the enormous range of features that have been encompassed within the entity of RSD (table 1), most of which were described in Mitchell"s classic account. It is difficult to imagine how a single disorder could account for so many disparate components. For example, one patient's affected limb may be pink and warm, but in another patient the limb may be cold and blue, and in yet another there may be hyperhydrosis but no colour change. One patient may have one of the many different forms of involuntary movements,[11 12] whereas another may have contractures in an immobile limb. Furthermore, particular forms may be seen, such as the shoulder-hand syndrome,[13] the RSD of children in which the lower limbs are particularly involved,[14] and transient RSD in pregnancy.

The variety of clinical features suggests that multiple processes perhaps subserve the entity of RSD, or that several different conditions may masquerade as a single entity, or that different phenomena occur at different stages in the illness.

TEMPORAL FACTORS

The clinical features of RSD often change with time.[13] Typically after a peripheral injury—for example, wrist fracture—the affected part is warm, red, puffy, sweaty, and painful. After some weeks or months the part becomes cold, blue, and dry, and remains painful. A third stage may ensue in which there is an atrophic, functionless, and still painful limb. These stages do not all occur in an individual patient, the time scales vary considerably, and even in the same patient the clinical features may change, sometimes day by day. It seems likely that different phenomena seen at different times are subserved by different mechanisms, and an example of changes that occur early and affect the cutaneous microcirculation is discussed below.

CONTRIBUTION OF VASCULAR AND MUSCULOSKELETAL PHENOMENA

As well as pain and various sensory disturbances, there are often features which suggest vascular and musculoskeletal components, and these variable components doubtless contribute to the heterogeneous clinical phenomena.

The warm, vasodilated limb often seen in the initial stages of RSD has been referred to earlier. Evidence from some studies indicates that these features could be due not necessarily to neurogenic inflammation but alternatively to loss of cutaneous vasoconstrictor activity at the spinal level, leading to disturbances of the skin microvasculature.[15] This sympathetic inhibition resolves after the early stages of RSD. These *vascular* phenomena may be nonspecific as they are normally seen after most injuries. It is also unclear what relevance, if any, the physiological changes have to the generation of pain, particularly when pain becomes chronic in longstanding RSD. Secondary mechanical factors, however, may contribute. Thus some patients' pain is influenced by whether the limb is elevated or dependent, presumably as a result of altered tissue perfusion or local engorgement. Furthermore, pain can occasionally be temporarily relieved, long before impaired nerve function develops, simply by applying a sphygmomanometer cuff to the limb.

Changes in *bone* were first recognised radiologically by Sudeck. They are due to osteoporosis which is typically spotty and affects the juxta-articular regions, but which may spread sometimes to affect much of a limb. Altered bone blood flow and effects of neuromodulators released locally may be important. Changes in bone and soft tissues are often assessed by various forms of isotopic bone scanning, and occasionally MRI, which may prove to be a particularly informative technique.[16] Unfortunately, just as with radiographs, the findings may be difficult to interpret, are non-specific, and are very dependent on the stage of the disease.[17] Even sympathectomy can result in a bone scan that resembles RSD.

Skeletal muscle may show increased temperature and blood flow in the acute stage, impairment of high energy phosphate metabolism, and reduced oxygen consumption,[18] and in end stage disease non-specific histological abnormalities can occur. The relevance of these findings is unclear.

What is now termed RSD was postulated to be a pseudoinflammatory condition 100 years ago, and histological changes around affected *joints* were recognised over 40 years ago.[13] The changes affect the synovium, in which there are abnormalities of collagen and small blood vessels and a cellular infiltrate. Scintigraphy using

labelled indium has demonstrated juxta-articular changes, but these seem to be pseudoinflammatory in nature.[19] Patients do not have a fever, and haematological and biochemical investigations and tests of immune function are normal.

THE VARIETY OF UNDERLYING CAUSES

The underlying causes said to lead to RSD are so numerous as to defy any meaningful attempt at analysis.[1 4] Various diseases of the peripheral and central nervous system can cause RSD, including stroke, multiple sclerosis, spinal trauma, and shingles. Systemic diseases including myocardial infarction and cardiac surgery, and drugs including phenobarbital, can also cause RSD, and the occurrence of the condition in children and during pregnancy has been mentioned above.

Evidently there is no single, specific aetiological factor, but undoubtedly the most common event leading to RSD is trauma,[1] both accidental and surgical, which is said to account for perhaps half of the cases. However, even this is contentious, because peripheral trauma appropriately gives rise to pain, together with features such as swelling and vasomotor changes; it is thus arbitrary when this process is considered too long lasting or too excessive to be normal, and the question of definition arises again, doubtless accounting for the great variation in quoted postsurgical incidence of RSD. Florid RSD after trauma is obviously very uncommon; whether there is a genetic predisposition is unknown, although compared with controls patients have an increased prevalence of the HLA-DQ1 histocompatability antigens.[20]

Is RSD a non-organic disorder?

Although prolonged pain and disability not unnaturally may induce psychological and psychiatric sequelae, there has been a view that at least some patients manifest a somatoform disorder, perhaps particularly when involuntary movements such as dystonia are present.[21] The contribution of placebo responses and effects of sometimes numerous therapeutic interventions can add further uncertainties. Because trauma is such a common cause of whatever RSD is thought to be, litigation often lurks, and rarely the malingering patient has been unmasked by covert video surveillance. Although psychological dysfunction in patients with RSD seems to be little different from that in patients with other chronic pain states,[22] all these aspects inevitably pose difficulties when the very nature of RSD is unclear.

Is RSD a peripheral, central, or combined disorder of the nervous system?

Reflex sympathetic dystrophy typically affects the periphery, particularly distally, and changes which may be florid often affect a hand or a foot. Yet changes sometimes spread proximally up the limb or even more extensively and follow neither a peripheral nerve nor root distribution. There may be involvement of the contralateral limb in a mirror fashion. Such features suggest that even when the initiating cause is peripheral, sometimes the subsequent course necessarily implicates the CNS at the spinal level.[4] Furthermore, the loss of vasoconstrictor activity referred to above,[15] the presence of hyperhydrosis,[23] and the development of urinary dysfunction,[24] all suggest a central component. When involuntary movements such as tremor or dystonia are present,[11 12] CNS involvement at the spinal level again seems inescapable, although higher and in particular thalamic levels could also be involved.

Of particular interest is that SPECT of patients with RSD discloses involvement of the contralateral thalamus, and furthermore that thalamic perfusion changes over time, initially increasing and then decreasing over months.[25] This finding suggests that adaptive changes in the CNS occur, and may go towards explaining the evolution of the clinical features.

Is the sympathetic nervous system involved?

This question has had profound implications for the management of RSD, and led to an enormous amount of both clinical and experimental research. Here, in particular, there are different views.[4 21 23 26] Some of the reasons for these different views are summarised below, but as a preface it will be apparent that the postulated involvement of the sympathetic nervous system originated from two clinical suppositions: the patient's limb shows features that apparently resemble sympathetically mediated phenomena; and pain is alleviated by interrupting the sympathetic outflow to the limb. Both these suppositions have been questioned.

CLINICAL FEATURES ARE NOT TYPICAL OF DISORDERS AFFECTING THE SYMPATHETIC SYSTEM

The clinical features of RSD clearly do not resemble those usually associated with diseases of the central or peripheral autonomic system, and RSD has even been described in a sympathectomised limb. Nevertheless, as discussed above, transient inhibition of segmental vasoconstrictor tone leading to peripheral vasodilation can occur. There are likely to be many other factors, including effects mediated by various neuropeptides and inflammatory mediators released from afferent nerve terminals and from damaged blood vessels and other tissues.[4] Many of these substances affect vascular permeability and hence fluid extravasation, and probably contribute to sensitisation of peripheral nociceptors producing pain and the various sensory disturbances.

Contrary to longstanding dogma, the sympathetic system is not hyperactive.[23] Microneurographic studies on sympathetic nerve fibres of patients with RSD are normal. Indeed, not only the impaired peripheral vasoconstrictor responses, but also the reduced concentrations of catecholamines in blood draining the affected part, suggest that the sympathetic system may be hypoactive. Denervation hypersensitivity may result and account for the increased density of α1-adrenoreceptors found in

skin and blood vessels, and for coldness in an affected limb.

BLOCKING THE SYMPATHETIC OUTFLOW RARELY ALLEVIATES RSD

Although sympathetic blockade seems illogical when, at least in the early stages, there is already loss of vasoconstrictor tone, interrupting the sympathetic innervation by various means has been practised for decades. Surgical sympathectomy is now rarely performed. Blocking the sympathetic outflow with local anaesthetics or rarely neurolytic agents, thermocoagulation of the stellate ganglion, ultrasound, and opiates applied to the ganglion have all been tried. In the past 25 years, sympatholysis by chemical removal of noradrenaline (norepinephrine) in the periphery has been carried out by (unlicensed) regional intravenous injection of agents such as guanethidine, bretylium, and phenoxybenzamine. More recently, the short acting intravenous phentolamine challenge has been devised as a predictive test for the efficacy of sympathetic blockade, but the validity of this approach remains controversial.[21 26]

All these procedures have potential side effects ranging from the trivial to the life threatening. Do they work? Only in the past few years has this issue been objectively addressed, and evaluation of many patients treated with sympathetic blocks or regional chemical sympatholytic procedures has shown efficacy to be no better than with placebo.[27] This conclusion, however, does not preclude *individual* patients from obtaining pain relief, and it has been suggested that pain relief then sometimes occurs due to blocking fellow-travelling afferent fibres.[28] These are presumably those same afferents which, when damaged or diseased, may *induce* pain (sympathalgia).

MISMATCH BETWEEN THE LABORATORY AND THE CLINIC

Although blocking the sympathetic innervation only rarely alleviates pain, paradoxically there is much experimental evidence suggesting that the sympathetic nervous system may have an important influence on the afferent nervous system, but perhaps only after nerve injury (for review see Baron *et al*[23]). For example, the afferent barrage is increased by sympathetic stimulation or by local noradrenaline. Furthermore, there is evidence in experimental animals that after nerve injury there are potential sites of novel sympathetic-afferent nerve interaction, the nature of which is currently being explored but which might include the expression or up regulation of functional adrenoreceptors on primary afferents. These sites of interaction include the cutaneous nociceptor, the neuroma, and the dorsal root ganglion where sprouting of sympathetic postganglionic fibres forming basket-like terminals around somata has been described.

That the sympathetic nervous system plays a part in nociception receives support from experiments in humans, including the rekindling of pain by iontophoresis of noradrenaline into a limb made pain free after a sympatholytic procedure, the exacerbation of postherpetic neuralgia by intracutaneous epinephrine and phenylephrine, and the induction of pain by electrical stimulation of the sympathetic outflow in patients with pre-existing causalgia. On the other hand, the evidence that sympathetic activity mediates pain, hyperalgesia, and vasodilatation induced experimentally in humans by capsaicin remains inconclusive.[26]

Why, when laboratory data predict that benefit might occur, is sympathetic blockade often ineffective in the clinic?[27] Apart from technical issues such as completeness of blockade, there are various possible explanations, including the fact that experiments on animals are simply not valid models for the human disorders, that patients with pain from damaged nerves do not react in the same way as healthy subjects undergoing a short lived experiment, and that sympathetic involvement only applies to certain patients with pain.

Are there treatments for RSD?

There seems to be no consistently satisfactory treatment for the pain, although the need to achieve mobility of the affected limb whenever possible is generally accepted. Physiotherapy and related techniques that aim to restore function are thought, but not proved, to be a prerequisite for improving pain. Unfortunately in practice this endeavour is often frustrated by the pain itself.

Apart from physiotherapy and the sympathetic blocking procedures referred to above, there are numerous reports of other successful drug, physical, and psychological treatments (for review see Wasner *et al*[29]). Drugs tried include opioids, tricyclic antidepressant drugs, sodium channel blocking drugs such as mexiletine and carbamazepine, GABA agonist agents, drugs such as gabapentin acting on calcium channels, anticholinesterases, calcitonin and griseofulvin, steroids, and adrenoreceptor and NMDA receptor blockers. Stimulation procedures include acupuncture, transcutaneous electrical nerve stimulation and peripheral nerve, spinal cord, and deep brain stimulation. Although a recent study indicates that spinal cord stimulation may be beneficial, the authors used modifications of the standard diagnostic criteria, over half the patients referred were excluded for various reasons, follow up was for only 6 months, there was no improvement in functional status, and this expensive technique had a 25% complication rate.[30] In another recent study, intrathecal baclofen was reported to improve the dystonia associated with reflex sympathetic dystrophy in seven highly selected women;[31] botulinum toxin rarely seems helpful. Hardly surprisingly, in view of the difficulties and risks of many forms of treatment tried, increasing attention is being given to cognitive behavioural and other psychological techniques which aim to help the patient deal with their pain rather than to cure it.

No treatment method has stood the test of time, none of the drug treatments is licensed for this purpose, and claims of benefit usually remain unconfirmed. Of interest, therefore, is the start of novel approaches to tackling the

pain. High dose vitamin C with its antioxidant properties has been used to try and prevent RSD developing after wrist fracture.[32] The role of bisphosphonates is also under investigation, and followed from their use in treating painful bony conditions such as Paget's disease and bone tumours.[33] If similar in their action to certain other agents acting on bone resorption,[34] bisphosphonates may relieve pain by effects on nociceptive primary afferents in bone and pain associated changes in the spinal cord.

Conclusion

Returning to the questions posed at the beginning, the definition, nature, and treatment of RSD remain unclear. I suspect that this is because many different physical and perhaps psychiatric disorders are included under the umbrella of RSD, each with its own underlying mechanism(s) and potential for specific treatment. There are clues that a more selective approach might be more fruitful. For example, it may be that only certain patients are helped by sympathetic blockade, and those with dynamic mechanical[27] or cold[23] allodynia are possibly more likely to benefit. In other patients, the presence of osteoporosis might theoretically predict a beneficial response to bisphosphonates,[33] and perhaps those patients with prominent pseudoinflammatory features might respond to steroids.[13] Rather than drawing conclusions from studies of large numbers of patients with heterogeneous disorders of different durations, detailed evaluation of highly selected components of RSD may lead to further understanding and better treatment. The ultimate achievement would be to prevent RSD developing.

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