Proceedings of the Pain and the Sympathetic Nervous System Symposium, Budapest, Hungary, 29–31 August 1999

Contents

1. Animal and human models of sympathetically maintained pain

W. Jänig

Kiel, Germany

Let me start based on general categories of pain along the lecture given by Martin Koltzenberg. He categorized them in this way.

I. Transient pain

Pain under biologic conditions, nervous system intact.

II. Persistent pain

For example, chronic pain after tissue damage or during inflammation. It is important to note that the nervous system is intact. As far as the chronic pain is concerned, it is pathological pain, and, most likely the complex regional pain syndrome I (CRPS) belongs to this category of pain. I will come to this later, because pain in this type of patient is dependent on sympathetic nervous system. These patients give very little indication that the nervous system is damaged.

III. Neuropathic pain

Journal of Back and Musculoskeletal Rehabilitation 14 (2000) 29–69
ISSN 1053-8127 / $8.00

Occurs in lesions of the peripheral system or Central NS. It is chronic and it is a type of pathological pain. Patients with CRPS II most likely belong to this category of pain.

In order to investigate the sympathetic nervous system in the generation of pain in these groups of patients and in order to understand the mechanisms of the sympathetically maintained pain one has to start from the clinical conditions and then design various types of human or animal models (the human model is an animal model – nothing special about human model except that there is the advantage that you can communicate with a human being).

Clinical observations on human beings after interventions, such as blockade of the sympathetic "chain" with local anesthetics or other ways allow us to develop a hypothesis, which may lead to the design of various types of animals models, e.g., Behavioral animal models, or what I call reduced animal models in vivo. For example, these are animal models in which you record in vivo from afferent neurons, sympathetic neurons, and so on. This may lead to further reduced animal models in vitro in which animal tissue, like the dorsal root ganglions with attached nerves, is put in the chamber or one can work on isolated cells in vitro. You have just heard from Dr. McLachlan how these studies are done. These types of studies are combined with other studies using morphological and other techniques.

I would like to concentrate now on mechanisms of sympathetically maintained pain. As I have mentioned, experiments which have been designed to investigate these mechanisms are based on clinical observations. This is important. If we didn't have the clinical observations, we would never investigate this question. It would never occur to us to investigate the relationship between the sympathetic postganglionic neuron and the afferent neurons under these pathological conditions. Under normal circumstances there is no obvious functional relationship between the sympathetic neuron and the afferent neuron. This relationship of sympathetic afferent coupling can occur at various sites of the primary afferent neuron and the sympathetic neuron. It can occur on the peripheral lesion site. In theory it can occur in the DRG and you have heard from Dr. McLachlan the changes which may occur in the DRG following peripheral nerve lesion; morphological changes and I will give you an example about possible functional changes that I also believe can occur along the whole nerve – this has never been tested. I would like to emphasize that this kind of coupling is dependent on activity in the sympathetic postganglionic neurons, and this coupling may be mediated by adrenoreceptors in the primary afferent neurons, but it may also occur indirectly via the vascular system.

The general overall mechanism of the generation of pain in these two groups of patients, CRPS I and II, is in the periphery and we may have some sort of changes of the nociceptor. We call this nociceptor sensitization. . . This may occur in the CRPS I patients. We may have changes of the nerves, e.g., in CRPS II after nerve lesion–nerve pathology. You have just heard what changes can occur in a peripheral nerve with large diameter and small diameter peptidergic and postganglionic fibers after a nerve lesion, distal to the nerve lesion and up to the DRG. These changes in the periphery lead to changes in the central nervous system which we call global centralization or central hyperexcitability. What is important is the idea coming from clinical observations that the efferent sympathetic outflow may be involved in the generation of pain. This establishes some positive forward connection which maintains, in the periphery, ectopic stimulus in lesion nerve fibers and possibly, and we have no model for this, sensitization of the peripheral nociceptors. This is the basic idea. I will concentrate on ways of coupling here in the periphery between efferent sympathetic fibers and afferent neurons. Tomorrow we will discuss changes in patients with CRPS I and II – changes of activity in the sympathetic neurons which may contribute to this coupling as a component of the central changes. These changes not only occur in sympathetic neurons but most likely in motor neurons and in what I believe is part of the neuroendocrine system.

Human experiments from the Uppsala Group (published years ago by Torebjörk et al.) performed with patients with CRPS II (chronic patients with pain dependent on the sympathetic activity nervous system for 5–10 years). One example: A patient had mechanical allodynia, cold allodynia and spontaneous pain in the hand. This allodynia was generated by stimulation of A beta-fibers from the skin. The cold allodynia pain was elicited by cooling down the skin to 20 or 25 degrees. These three pains – the spontaneous pain, cold and mechanical allodynia, were abolished after blockade of the stellate ganglion. The block of the stellate ganglion was assessed by measuring the skin temperature as it increased to about 36°C. Now these authors ask the question whether they can rekindle the pain under the conditions of stellate ganglion block by injecting noradrenaline. The idea was simple – this pain is dependent on activity in the sympathetic nervous system, and, implicit in this is release of noradrenaline.

So they injected noradrenaline in the skin and could elicit mechanical allodynia, spontaneous pain and cold allodynia. It is important that after the stellate ganglion blocks, sensation (cold, warm, touch) were entirely normal, so the block did not affect the afferent fibers. What can we learn? This experiment clearly shows that activity in the sympathetic postganglionic fibers is involved in maintaining activity in nociceptors. Second, we have to conclude that primary afferent nociceptor fibers have expressed in some way, adrenoreceptors; otherwise, the communication between the postganglionic neurons and the afferent neurons would not work. Third, we have to conclude that this coupling occurs in the periphery.

Before these measurements were done, we had done some interesting cat experiments 12 years ago – (we call it the Experiment of the Year) by Häbler and Koltzenberg and myself. We performed a cross connection between sural nerve and tibial nerve in the cat. The sural nerve fibers sprouted into the distal stump of the tibial nerve and into the territory of the tibial nerve. After one year we tested whether the fibers in the sural nerve could be activated by electrical stimulation of the sympathetic chain ganglion. We found unmyelinated fibers, which we could not localize; we don't know whether they are nociceptors or not. They were definitely unmyelinated afferent fibers which could be activated by stimulation of the sympathetic chain at very low stimulation frequencies (1, 2 3 and 4 hertz). These are frequencies which you find in postganglionic neurons which innervate blood vessels in skin or skeletal muscles. These are the stimulation artifacts here, and the recordings from the unmyelinated afferent fibers isolated from this lesioned nerve. We got activation at 2 hertz, massive activation of the afferent fibers at 3 hertz, and so on. IV injection of adrenaline also led to massive excitation of these fibers. We could show in this experiment that the vasoconstriction induced by adrenaline is not responsible because angiotensin did not do anything. Angiotensin generates a massive decrease of bloodflow and vasoconstriction. So in theory this type of experiment is fairly consistent with the data from the patients in the Uppsala group. We have done other types of experiments that confirm this.

Both sets of experiments in human and in animals were done under chronic conditions – the amazing thing is that under chronic conditions in the human and the animal the state is obviously stable (the sympathetic afferent coupling). Now, some functional studies of sympathetic afferent coupling of the DRG. The whole story of synaptic coupling of the DRG started with experiments I did with Marshall Devor in Israel. And these physiological experiments then started all the morphologic work done by Elspeth McLachlan, and others such as the group from Galveston. We were extremely excited by the neurophysiology and even more by the morphology and I will show you the general results. A reminder; we used spinal nerve lesion and sciatic nerve lesions. The Galveston group used the ventral ramus of the spinal nerve. First the perivascular noradrenergic fibers start to sprout around DRG cells. This is a somewhat complex experiment. It was done to test whether the coupling between the sympathetic neurons and the afferent neurons occurs in the DRG. We recorded the sciatic nerve lesion from this axon and identified them by stimulation of the dorsal root.

Then we tested whether these afferent fibers can be activated by electric stimulation of the sympathetic chain. Here you see an experiment with the blood pressure representing the activity in an afferent fiber. After the sciatic nerve lesion or spinal nerve lesion many dorsal root ganglion cells generate ectopic activity. Under normal conditions when there is no lesion 99.9% of the DRG cells do not generate activity. When we stimulate the sympathetic chain at 2–5 hertz this afferent DRG fiber was activated. The same occurs when we injected adrenalin (a microgram) in the rat. Here you see the activation. In this experiment we investigated which adrenoreceptors were involved because we were deeply convinced that this is directly adrenoreceptor-mediated. First we applied an alpha 1 adrenoreceptor block with prazocin and you see almost nothing happens. Because we blocked the alpha 1 adrenoceptor we have almost no vasoconstriction and very little increase in blood pressure. Then we blocked the alpha 2 adrenoreceptors with (yohimbine) and here you see the response is gone – and also the response to adrenaline. These results have been published. We were content with the results, which showed the alpha 2 adrenoreceptors are involved in this kind of coupling, and there is very little alpha 1 adrenoreceptor activity. However, we became somewhat skeptical about these results. In Kiel we did various experiments and this has also been done by Sebastion Effenfelder and Joachim Häbler. They found out that the activation of the afferent neurons is very closely correlated with the increased resistance and decreased blood flow in the dorsal ganglion. In an almost identical experiment, the spinal nerve lesion model, you see the activity in the dorsal root fiber, the arterial blood pressure, and the blood flow measure with the laser Doppler and the peripheral resistance, and here you see the frequencies or stimulation of the

sympathetic chain. This is very closely correlated with increased resistance or decrease in flow. This is not a proof that the sympathetic afferent coupling in the DRG is directly mediated via the vascular bed but it is a strong argument that this is the case. This coupling may occur indirectly or directly via the vascular bed. These ideas are fully consistent with the data which have been presented by Dr. McLachlan about the innervation of endoneural blood vessels and blood vessels in the DRG after nerve lesions. At the same time the group from Galveston in 1994 presented a very interesting behavioral model of mechanical allodynic behavior. They lesioned the ventral ramus of the spinal nerves L5 and L6 (ligated them). These rats develop a mechanical allodynic behavior stimulation. When you stimulate the paw with different Hertz, you measure the frequency of the incidence of paw withdrawal. Here – the lesion was done at time zero, and then this mechanical allodynic behavior develops. This is reproducible in almost every animal in every laboratory that has used this model. However, the Galveston group then tested the sympathetic nervous system involved in this. They sympathectomized the animals surgically. And here you see the behavior almost disappears. Here, after 5 weeks it does disappear. Here, sympathectomy first, then they lesioned the ventral ramus of the spinal nerve, and the behavior never develops. A very convincing experiment.

Various groups were excited by these data. We and Dr. McLachlan initiated a joint grant, and the Baltimore group initiated a big research project along with others based on this model. The first thing we did was to reproduce these data. It shows the problems we have in our experimentation which are not dissimilar to the clinical problems clinicians have with their patients. We repeated these experiments in Baltimore and Kiel independently. We tried two different strains with different testing methods. In Baltimore, the animal tester was blinded. To our surprise and disappointment, we could not show that the sympathetic nervous system is involved in this mechanical allodynic behavior. Here you see the exact same experiments – the allodynic behavior develops. Here on day 7 after surgical sympathectomy, no change at all. Here we measure paw withdrawal of the rat in absolute milliNewtons (under normal conditions the rats withdraw their paw at 150–180 milliNewtons) and you see here the mechanical allodynic behavior, and after sympathectomy, no change at all. And here we did the sympathectomy first and then we tested the behavior, and the behavior fully develops. In Baltimore and Kiel we got identical results. This doesn't mean that we refuted the data from Galveston, but the question is what had been done in the experimental animals in Galveston, and we have to find this out; it may give us an interesting insight into the role of the Sympathetic nervous system in generating this type of behavior (or not).

We went a step further and took systematic measurements of the ectopic impulse generation in these rats in the dorsal root in the activity which is seen in the spinal cord. This is ectopic activity in the rats with respect to time after the lesioning of the L5 spinal nerve in sympathectomized animals. You see there is no difference between the sympathectomized animals and the normal animals in ectopic activity. Here is paw withdrawal threshold in milliNewtons (150–180); no difference between sympathectomized and normal animals. Here there is a weak correlation between activity and paw withdrawal threshold. These data appear to be disappointing, but we have to think about these experiments in relation to those done in Galveston in order to understand what's going on.

What I have told you is related to patients with CRPS II. I will show you an example you all know. A patient with CRPS I (a patient with a minor lesion, and no obvious nerve was involved). This patient developed classic reflex sympathetic dystrophy, with deep hyperalgesia, swelling and so on. This is the same patient three weeks after treatment with sympathetic blocks and therapies. The swelling, pain and vascular changes were gone. It is generally believed that in these patients the sympathetic nervous system is also involved in the generation of the pain and some of the allodynia and other changes. However, the mechanisms just discussed cannot account for it. Now this is an essential experiment done by Donald Price and his group. The argument is that the sympathetic blocks and the relief of pain is not related to the activity of sympathetic neurons, but to placebo effect. What they did in a CRPS I patient is they tested saline vs a local anesthetic . With saline, you get relief in a double blind trial. You get significant relief of pain for one to two hours. With the same patients with local anesthetic you get relief for days. For me, this is clear proof that the sympathetic nervous system must be involved in the generation of pain with these patients. However, I must say we don't know the mechanisms by which the sympathetic nervous system is involved we don't know. We have to start form the beginning and develop other animal models as we have done so far in order to understand what is going on this large group of patients.

2. Changes in the sympathetic and nociceptive neurons and in neurovascular transmission after nerve injury

E. McLachlan

Sydney, Australia

I have worked with the sympathetic nervous system (SNS) for 30 years.

I want to talk about some of the consequences of peripheral nerve lesions on sympathetic neurons in experimental animals. I hope that the changes in the sympathetic nervous system (SNS) that we see may be helpful in your work dealing with clinical syndromes.

I've included the nociceptor neurons because the sympathetic and nociceptor neurons, have a common ontogenetic origin and a common dependence during development on the neurotrophins, particularly nerve growth factor. In the adult, nerve growth factor dependency is retained by sympathetic and by peptidergic nociceptor neurons, ie, by neurons containing substance P and CGRP. Today, I'll show you histochemical data demonstrating noradrenalin and tyrosine hydroxylase – one of the enzymes that makes noradrenalin – as markers of sympathetic neurons and their terminals and immunohistochemistry for substance P and calcitonin gene related peptide (CGRP). I will also mention some functional data.

The experiments I'm talking about primarily involve lesions to hind limb nerves and tail nerves in the rat. We've made lesions of peripheral nerves, sciatic nerves or the tail nerve, and in a few cases the spinal nerve close to the dorsal root ganglion (DRG). And there are two types of lesions we've made – complete transsection with ligation in order to generate a neuroma – to see what happens to neurons which are completely unable to regenerate. And also cryosurgical lesions or crush lesions of the peripheral nerve which facilitate regeneration – and after which neurons with myelinated fibers completely reinnervate the periphery in experimental animals. Most of the material I'm talking about concerns the innervation of the vasculature, which is the most widely distributed organ of the body which receives sympathetic innervation.

The first few experiments concern the potential for regeneration in this system. This slide shows some sections of the rat tail artery – long and straight, and you can denervat the nerve trunks close to the base of the tail. The artery extends along the length of the tail, so you can determine precisely how far away from the lesion you're looking. In a way the tail is a regulatory organ – its innervation is very similar to innervation of digits in humans. The main tail artery is particularly dense in these cutaneous vessels. On the left you can see sections of control arteries, on the right, sections from vessels where the nerves have been frozen and the axons allowed to regenerate. If we look here it's about 5 cm beyond the nerve lesion – as early as 50 days after the lesion there's a sparse, but beginning to look quite normal, reinnervation of the artery. By 150 days there's a very reasonable perivascular plexus with the same complex criss-crossing of varicose noradrenergic nerve terminals. You'll see that even after this time – the density of this plexus is less than the density of the age-matched control. And in fact if we follow for periods over a year we find that the density of the reinnervated plexus never achieves more than a maximum of about 80% of the density of the control. Now this is 5 cm from the lesions – and we'd regard this as pretty good reinnervation – and this is under a circumstance where there is very little to prevent the axons from regenerating. You can calculate that the rate of regeneration is approximately 1 mm per day.

The next slide shows what happens more distally in the tail. This is 11 cm from the lesion. The normal artery at this distance is a little bit smaller and we find that even this long time, several months after the lesion, the longitudinal section of the artery shows absolutely no sympathetic axons. All you can see here is part of the internal elastic lamina in this section. In fact, beyond about 10 cm from the nerve lesion we find extremely poor reinnervation – there are very few axons. But this only applies to the main artery. If we look below at these other sections from the same region of the tail – longitudinal section through the tail artery –but part of the arteriovenous anastomosis (AVA), which sits beside the artery – and these AVAs are present in the distal part of the tail. On the right hand side, again, several months after the lesion you can see that the AVA is extremely densely reinnervated, and this happens very fast – I could have taken the same picture at 50 days. And this section at the bottom – the adjacent artery which has only one little axon here associated with it – this is the internal elastic lamina. So there's very specific reinnervation of different targets. The blood vessels are reinnervated very poorly; the AVA and sweat glands are reinnervated very effectively. So there's something special about blood vessels. There is poor anatomical reinnervation – what about function?

We've done some studies which suggest that reinnervation of the vessels even with very few nerves is very

effective. But there are some other experiments done in other species which I'd like to tell you about. The next slide shows you an experiment done in Jänig's lab – concentrate on top traces – done by Martin Koltzenberg and Joachim Häbler. They show changes in blood flow evoked by stimulation of the nerve in the cat paw pad, and the flow is measured with a laser Doppler – downward deflections are vasoconstriction, and this is the stimulation pattern. You can see the marked vasoconstriction produced by stimulation of the sympathetic nerves. This trace here comes from the contralateral paw pad in which the paw was reinnervated by axons of the sural nerve – not the original nerve supply – and I should point out that the sural nerve is much smaller than the tibial nerve – to which it was cross sutured, so the number of axons available for reinnervation was few. You see the responses are at least the same size, if not larger, and are prolonged. A few years ago Masefield and I did a similar type of study in humans. This shows laser Doppler records from the foot skin of a 32-year old woman after a tibial nerve graft – several years after the graft. You'll see on the resting conditions, on the normal innervated side there are big swings in blood flow which vary with conversation in the lab – we tried not to make too much noise, but there were a lot or responses in the skin vasculature. But these are absent on the reinnnervated side. On the other hand, at this arrow here, we made a very loud noise, a classical stimulus for the sympathetic nervous system, and activation of the SNS produced a very marked and almost complete shut off of flow on the normal side for this period of time. You'll notice there was a vasoconstriction also on the reinnnervated side, but there was a lag before it occurred, the onset was slower, and in fact the vasoconstriction persisted for very many minutes. So there was a response, we believe to only a few axons, but it was very sluggish and it persisted for a very long time. Perhaps I could summarize those findings so far.

After a nerve lesion, there is very poor reinnervation in an anatomical sense. But the target tissue – the blood vessels – remain hyperreactive and the responses to nerve activity can be a little abnormal but certainly quite large.

While we were looking at these sections we also examined them histochemically – for peptides. The next slide shows some sections of the tail artery – longitudinal sections you can see the wall thickness here so this is through the middle of the artery – this is the lumen. And these are pairs of sections taken relatively proximal and going more distally along the length of the tail. These have been stained for tyrosine hydroxylase (TH) and CGRP and we can visualize the perivascular plexus with two different filters in the same section. On the left you can see the reinnervation by TH axons is very good, and as we go distally there are rather few TH axons. In the same sections, staining for CGRP, stains the nociceptors, and we were quite surprised because in this artery there are hardly any peptidergic axons normally, but in the reinnervated artery there were CGRP axons which increased in density as we went peripherally. What this tells us – there is in conjunction with the slight sympathetic reinnervation, there is an overgrowth of nociceptor fibers – peptidergic nociceptor fibers – to the blood vessels. We don't really know the functional consequences of that.

Another thing we saw in these sections in the amount of TH seemed to be less, and decided to see what happens in the nerve trunk, in lesions associated with neuroma formation. You're aware that there's functional evidence that sympathetic activity can activate sensory neurons projecting into a neuroma and there's extensive literature suggesting that there is sympathetic sensory coupling within the neuroma itself. The next slide shows the results of our experiments in animal tissue. This is a section staining for noradrenaline, and this a section of the neuroma – these bits of light staining are primarily mast cells – and other invading cells – this the autofluorescence of myelinated axons, and you can't see, but there are a few fine noradrenaline fibers. Within the neuroma itself there's hardly any noradrenalin. We do see some in the connective tissue around the outside, some sympathetic fibers around the neuroma, but within the neuroma where the nerve trunk is there are virtually no sympathetic axons. And this picture – shows the drop in noradrenalin content in the neurons themselves. This is a section of the paravertebral chain ganglia which projects into this damaged nerve. This is the contralateral side, two ganglia fused – you can see cell bodies of noradrenergic axons which are normal . . . this is the side which projects into the neuroma and there is hardly any noradrenalin in the cell bodies. We thought we'd look at this more carefully by enhancing the noradrenalin content. So we cut the nerve trunk when the animal was anesthetized before sacrificing, this allows the noradrenalin which is being transported distally to build up in the nerve trunks. You can see here we get a lot of build up of noradrenalin. At the cut ends of these nerves if we leave them cut for an hour or two before we perfuse the animal. This section is just 2–3 cm proximally, you can see there's quite a lot of noradrenalin normally in these cut axons. On the lesion side at the same sort of levels there are

very few noradrenalin axons detectable – even right back up toward the origin of the sympathetic ganglion. So basically there's very little noradrenalin in the nerve trunk provided the axons cannot regenerate.

The next slide – what we did see in the nerve trunks. The endoneurial blood vessels in the peripheral nerves in rat – and perhaps in humans – are not normally innervated. The control of the endoneurial blood flow is by epineurial vessels which are densely supplied by sympathetic nerves, and the nerves which penetrate inside of the nerve trunk have no axons on them – and we confirmed this in the rat. After the nerve lesion, particularly the neuroma, we found very large hypertrophied blood vessels, very densely innervated by sympathetic fibers, within the nerve trunk. These blood vessels were present close to the neuroma and back all the way to the dorsal root ganglion and close to the gray ramus itself. The brightness of these noradrinergic fibers, compared with the noradrinergic axons within the nerve trunk suggests that these sympathetic fibers are derived from outside the nerve and grow in with these new blood vessels. This hyperinnervation of the endoneurial blood vessels could have quite marked effects on the blood flow within the damaged nerve trunk. So we can say there is very little noradrenalin within damaged nerves provided the sympathetic axons can't regenerate. And, we can say there are hypertrophied vessels with a dense innervation. And the functional consequences of this I think Wilfred Janig will discuss.

That was quite a surprise to us to find this rearrangement.

Now the other place where sympathetic and sensory neurons are know to interact functionally is from experiments at least in the DRG. So the other place in which we looked – because we were tracking back toward the origins of these neurons – was in the DRG itself. The next slide shows two halves.

On the left we have a section from a normal DRG – edge of the ganglion in the rat you can find small vessels which have a noradrenergic innervation. These are the ganglion cells here, showing some autofluorescence. On the right side, you can see appearance of the ganglion about 10 weeks after ligation of the sciatic nerve. These are noradrenergic fibers which now run right through between the DRG cells and encircle some of them with this very dense plexus of noradrenergic nerve terminals. This was quite exciting, and looked like it might be a way in which sympathetic nerve terminals releasing noradrenalin might be able to modify sensory neuron activity. The next slide – the origin of these sprouts. This is the blood vessel at the edge of the ganglion with its normal dense noradrenergic plexus and sprouting from it you can see down here these long wavy axons that spread out and grow between the DRG cells. Now this is collateral sprouting of normal perivascular axons which have not been damaged by the nerve lesion, but there is some evidence that some of the axons that were cut project back and grow into the DRG as well. Now this growth suggested that there might be something that would attract growth of collateral sprouts, and such a factor would be nerve growth factor. In order to test this my colleague in Adelaide did an experiment in which he looked at the growth of tyrosine hydroxylase-positive axons in the DRG at different times after a spinal nerve lesion. When you cut the nerve close to the DRG this overgrowth with sympathetic fibers is very pronounced – this represents the total amount of TH staining he saw in unoperated ipsilateral and contralateral, in the lesioned ipsilateral and contralateral, and in two experimental groups.

What he did – because the nerve was cut close to DRG it was possible for a very dextrous pediatric neurosurgeon from China to put a very fine catheter and run it up into the DRG itself so that antibody to NGF could be applied directly to the sensory neurons. This antibody was supplied with a mini pump over two weeks – the effect was to reduce substantially the amount of sprouting within the ganglion. There's small amount of sprouting contralaterally and the contralateral sprouts were not affected by the antibody, showing that the effect was very local. The second experimental group – used an antibody to neurotrophin 3 which had at least as good an effect as NGF, but we don't know if it worked on a different receptor. But we can see that growth factors within the ganglion are responsible for the sprouting. Now because of this we thought that if NGF is up regulated that there should be sprouting also off the peptidergic nociceptor fibers. The next slide shows you that this is true – a micrograph showing an axon surrounding a large DRG cell in which the staining is pole localized for red substance P and green CGRP – no this is a nociceptor axon forming a very close connection with a ganglion cell. The next slide – origin of the nociceptor neurons. Here on left, stained with CGRP is one of these perineuronal baskets. This is a CGRP-positive small diameter neuron and this is the axon from that neuron branching around the large diameter axon. On the right the same neuron can be seem to contain flurogold, which is a retrograde tracer from the lesion site. We found that most, but not all of these neurons were actually the ones lesioned when the sciatic nerve was cut. The next slide shows the dimen-

sions of the neurons which carried these perineuronal rings. This is a histogram of sizes of DRG cells – the white columns are the normal size profile, most of the neurons in the ganglion are small diameter, but the perineuronal rings are formed around these large diameter neurons, the ones that are peptidergic and the ones that are sympathetic. So the next thing we can say is that in the DRG there are novel connections between sympathetic and nociceptor terminals and large diameter mechanosensitive neurons. Next slide – some of these axons containing CGRP are around the same neurons as ones with baskets containing TH. Examples, etc. But there are some neurons which have sympathetic axon but no peptidergic ones.

Next slide shows lack of localization, in this case, with TH. This neuron has no stained axons around it, and this neuron, adjacent, which has no TH axons, is very densely invested with varicose terminals containing synapapsin – a synaptic vesicle protein. By examining these colocalization studies we realize there must be another type of neuron that was sprouting, presumably sensorineuron, and we were able to show that there are very many of these perineuronal rings formed with neuropeptide gallinin, a neuropeptide which is upregulated in damaged sensory and sympathetic neurons.

This shows the time course of development of these perineuronal rings. This is days up to 4 months after a lesion, to over a year. Rings take several weeks to develop – peak around 12 weeks and then decline slowly in number, but you can still find sympathetic and peptidergic rings present well over a year. Also present after nerve lesions which permit reinnervation.

This summarizes changes. Nerve trunks after lesion contain atrophied, dying, unmyelinated axons from small diameter, sensory and sympathetic neurons. This means that within the nerve trunk the small diameter neurons that fail to regenerate tend to disappear, but we were able to find blood vessels which contained a lot of sympathetic axons all along the length of the nerve trunk and at the base of the DRG. Within the DRG there are novel connections with these large diameter neurons which are presumably mechanosensitive, and this suggests that there is some behavior of these sensorineurons which is modified by these terminals, although it's been difficult to demonstrate any functional connections at all. How can this connection be important for pain? Results from Clifford Woolf's lab a few years showed that it's precisely these large mechanosensitive neurons which normally terminate in the deep dorsal horn which sprout after nerve lesions and grow up to terminate in lamina 2, where the endings of the unmyelinated neurons have retracted in the same from the central terminations as they do from the distal ones after a nerve lesion. All of these changes may occur in humans. There are some reports in the neuropathology literature of these types of perineuronal structures, but the most important part is that we don't know much yet, and I suspect that the actions of the sympathetic nervous system on sensory neurons could just as easily be via changes in the blood flow through these large, hyperinnervated blood vessels.

Q. Are you sure when you see fibers with poor content of noradrenalin that it is really low content?

A. I would answer that on structural grounds. Noradrenalin in sympathetic neurons is normally only at very high concentrations in varicosities from which it is released. And the structures which we mostly see after the nerve lesion or fine smooth axons. Occasionally there is a growth cone with bright noradrenalin in it. When there is a varicosity or an accumulation of vesicles there is noradrenalin present. But we can't find varicosities very easily.

3. Pathological chemosensitivity of injured nerve fibers

L. Urban

London, UK

Our goal is to reveal whether there is any pathological chemosensitivity of injured fibers. What we were using was basically an axotomy model – to provide the same damage to all fibers. What we did after axotomy was to let the animal survive 8 to 21 days. So there was a severe nerve injury of the subacute type. What happens in the neuroma and in the DRG cells and particularly what happens to the sensory chemosensitivity of large fibers? Our study is based on large myelinated fibers.

We cut the sciatic nerve out and then the spinal nerve and associated DRGs with the dorsal roots put into an organ and centrifuged it continuously in a different chamber so we were able to apply different drugs to the neuroma and the DRG, and we recorded from the fibers, single fibers or small filaments from the dorsal roots. These data are fully known – but I would refer you to other references. It is important regarding behavior of fibers that we found in control animals none of the large fibers were spontaneously active.

In the sham operated animals – where we opened up the muscle and removed the sheath of the nerve, we

had about 1 percent of all the fibers. Numbers of fibers in all groups above 1,000 (a two-year study). To our surprise in those animals which had a neuroma for at least 10 to 14 days, we found only about 3% of the fibers were spontaneously active. This was a surprise.

Slide. In these 3% of fibers we could identify three different types, or patterns of spontaneous activity. First, at higher or lower frequency – present for hours. Considerable number of fibers with low frequency activity, but then spontaneous bursts develop. And this was infrequent-came in between 5 and 10 minutes, and then it went back to baseline activity again. We saw fibers which had only sporadic activity and these are all large unmyelinated fibers.

To summarize what we had. Basic data: The sporadic activity was the same in all kinds of animals (two kinds of rats). Surprisingly, when we did behavioral experiments in Selzter model we didn't see any differences in thermal or mechanical hyperalgesia between the two strains – so the significance of this remains unresolved.

What we wanted to know – whether these fibers were sensitive to any adrenergic agents. What we did was to use noradrenalin perfusion to the DRG in a concentration of 100–300 micromole, for five minutes. Some of the fibers responded quite vigorously to this perfusion, but the response was very slow. We wanted to examine this phenomenon further, that if we depleted noradrenalin from the existing content of noradrenalin in this system would it evoke any firing or increase of firing in these fibers? So if you apply tyramine to these cells or DRG or neuroma you can evoke an increased firing rate in certain cells. This is a summary slide. If you measure the ongoing firing – and this is the peak firing in frequency – these are the numbers of spikes counted in two minutes prior to the application of the drug and post drug application. In all cases, if you use tyramine, noradrenalin or UK 14304 – an alpha 2 agonist – you could see a significant increase in terms of firing. What was interesting for us – although we had a large number of fibers – was this summarized in the next figure.

These are the groups: Control, Sham and Neuropathic animals. Two groups of fibers – only 3 percent of fibers show spontaneous activity. The majority are completely silent. An interesting pattern. Tyramine, noradrenaline or UK 14304 doesn't activate fibers in control, similar in the Neuropathic animal. Never able to induce any activity by either tyramine or noradrenalin. Some by UK 14304 – but low amount of fibers. However, with fibers with a different kind of pattern? – largely fibers with ongoing activity – because it was much easier – then you see a tremendous increase in firing activity. In basically all of the fibers, about 90%. Similarity with all three substances (tyramine, noradrenalin, and UK 14304). From these data one can assume that there are two aspects of these experiments. One ... for certain reason, the spontaneously active fibers, generated in these damaged nerves, are more sensitive to adrenergic agents. However we have to remember that the number of these fibers are not high – a low percentage.

Obviously, what we examined here doesn't have any relevance in the periphery where you see the vascular effects, for example. I would like to emphasize that what we wanted to show, what kind of relationship develops between he sympathetic and the sensory nerves in the neuroma and in the DRG.

4. Therapeutic aspects of CRPS and SMP

P. Raj

Lubbock, TX, USA

The available data are not satisfying. E.g., from few studies do you see the number of patients who are cured from pain, nor those with pain relief. I would like to focus your attention on the difference between some of these.

Studies show that 50% of patients have remaining pain after l year, 5 years, and 10 years.

This slide shows important results from Dr. Gertzen, last year. About 70% of patients have evoked pain five years after treatment for CRPS. About half have problems with their joints. Nearly a third have problems 5 years after treatment, eg, with neglect-like syndrome. That means all kinds of treatments are ineffective in about 50% of patients.

Next slide: what is major complaint of patients with CRPS? This is a study from our working group – and we looked for changes in pain after limb positioning, ischemia and during movement. There are some data in the classification paper about CRPS that the elevated position will decrease the pain, lowering will increase, and ischemia will abolish the pain, and moving should increase the pain also. Today, there are no data in which these reactions are compared with other pain patients – e.g., after nerve injury without the development of CRPS. II. Both groups included about 25 patients for this, beside the marked increase of pain during mov-

ment. In the same group we analyzed the technetum99 uptake and the range of motion and you can see again the differences. The main ratio between the uptake on the involved limb, cf. the other side that the most increased ratio is close by the joints, not in the bones. There's nothing happening in the other group. This is the main difference between CRPS – not the changes of pain by changes of positioning. There's a very strong correlation between the range of motion of the involved wrist and the uptake quotient in the scintigraphic findings. This is a typical finding and can be explained by changes of the soft tissue blood supply or capillary leakage or by an inflammation process. This is a point of controversy up to today.

Slide. With this in mind I think there are some main therapeutic principles in patients with CRPS. First, treatment is not pain management only. 2. Treatment of CRPS must not be painful by itself – an old recommendation. There should be long-term treatment with a multimodal and inter professional approach. That is easy to say but hard to perform. This inter professional approach must be done concurrently, not after one or the other has failed. And, the next important point, the approach must be in relation to the stage of the CRPS and to the severity of individual complaints. that means that we need another staging concept. In Kiel, the group has proposed another staging concept-1, 2, 3, 4, only according to clinical features. Most important is pain – pain in absence of any somatic or sympathetic nerve block. Stage 1, patients with ongoing pain. Stage 2, pain not ongoing but with exercise or moving. Stage 3, patient without severe pain, rarely after exercise. Stage 4, without pain, but some impairments – movement muscle sense, problems like this.

Slide. The goals of the treatment will change depending on stage. First stage – free of ongoing pain and spontaneous edema. In this stage, we avoid every exercise treatment, physical therapy on the involved limb. Only on other side. Pain treatment as much as necessary. Physical treatment to include only immobilization, elevated positioning and night splints.

Stage 2. Pain treatment as little as possible. Careful transition to active mobilization.

Stage 3. Pain treatment not necessary at all. By wrong treatment, patient can fall back to previous stage, and you must repeat.

For details, in stage 1, but low severity, treatment options, immobilization, elevated positioning, night splints, analgesics, if necessary, maybe cold applications but no blocks. If patient is not free of ongoing pain we must repeat assessments in the coming weeks looking for pain and function. Then step 2 eventually.

Stage 1 with ongoing pain and high severity – or in failure of step 1 (pain above 3 on a numeric rating scale) or more important, of progressive loss of function, then other treatment options will be necessary.

We have to evaluate the significance or relevance of sympathetically maintained pain in this case. If yes, then repeated sympathetic blocks or opiate injections into the sympathetic chains, sometimes testing of the efficacy. Again, repeating assessments and new diagnostic procedures may be the transition to step 3 of the treatment. What means of evaluating SMP is not only important for patients with CRPS – pain diary, pain assessment, functional state, then we start with opiate injections or a conventional block of sympathetic chains – diagnostic – if pain relief is greater than 50% and lasts up to four hours, then repeated treatments are recommended. If not, advanced monitoring is necessary. I think there is a high risk to declare a patient as not having SMP and one reason for this may be anatomic variance (shown in poster) or inadequate technique of blockade. The problem is that normally we only look for the increase in temperature, and here I can show you another technique of continuous long term monitoring of skin temp that may lead to the misdiagnosis SIP. In this patient a stellate block led to a marked increase in temperature, but after a few minutes – after an hour the temperature had cleared. Show no pain relief. 24 hours later we performed the next blockade – the correct technique and we can see long-lasting increase in temperature. But if we had only looked for the first ten minutes for this temp we would have said this patient has not SMP – this patient went for a sympathectomy two months later and was cured of disease.

Next slide. Before we should say a patient does not have SMP in CRPS we need advanced monitoring. Increase of temperature gave no evidence for a total block. We have to measure sympathetic reflexes like vasoconstriction after deep breathing or after cold pressor test – a technique I've shown you before. Step 3 of treatment in stage 1 patients is to discuss other options. Surgical intervention may be effective in some, eg patients with CRPS as a manifestation of carpal tunnel syndrome. But in most cases we prefer sympathectomy. IN patients with CRPS II peripheral stimulation or spinal cord stimulation may be more effective. We avoid plexus blocks or epidural procedures but I know Dr. Racz prefers this. Amputation is the worst measure. I've included this slide – we have treated 165 patients with severe CRPS and in 11 patients – less than 10% – we've performed sympathectomy. All have been treated more than 6 months following the

stepwise ladder I showed you. All showed a marked decrease in pain – three have no pain but are functionally impaired (-2-6 months follow up only). Four patients have no significant improvement – CRPS II. In three of the four, we found no real sympathetic deficit – they have remaining sympathetic reflexes – meaning the sympathectomy was not effective enough. In stage 2 – without ongoing pain – the treatment options are changed. Marked differences from stage 1. Optimizing or reducing the strain of exercises, otherwise stop it and go back to step 1. Physical therapy, functional splints – in this stage we start with a topical application for one to four weeks-start with a high dose and then lower. This means we need other treatment options for stage in which ongoing pain is the main symptom. Here is a case report. First four weeks of rx with many blocks – then after a month we started with prednisolone, and with the blocks we could decrease the ongoing pain, but not to the same extent, the exercise pain. This is survey of this patient for a year. Reducing pain was easy in first weeks with aggressive treatment. Decline of exercise pain – we needed 40 weeks. But the beginning of the restoration is shown – more than one year. Now this patient is free of complaints. Example of treatment concept. We should discuss the goals of treatment. Which modalities and at which stage.

5. Regional anesthesia and interdisciplinary care: improving function in CRPS patients

P. Raj

Lubbock, TX, USA

This is a clinical session.

Greetings from Texas Tech. Reflex sympathetic dystrophy – a complex disorder, could develop due to minor or major trauma. Characterized by pain in the limbs – even though some are trying to diagnose it in the trunk. But I don't think so. Only extremities in my opinion. It certainly includes: autonomic instability, sensory abnormalities, motor dysfunction and trophic changes – how quickly is not known. Some people rapidly, and in some, the signs and symptoms are there and others are not. The active psychological disturbances are more like a chronic pain than anything specific to CRPS. Classical symptoms; swelling, edema, dysfunction, pain on movement of the interphalangeal and metacarpal joints. Interesting story – lady 7 months pregnant, was shot in her axilla with medium nerve injures, following which she developed CRPS II. If somebody touched this hand she would get extreme pain there, so this is a crossover from one side, stimluation to the other side. Of course it can be early, so I can't say what stage it is, but it is early because there is some discoloration occurring, pain, and some allodynia, and it can go on to inflammation, etc, and could be a complex of CRPS. What is the goal? We feel it is functional restoration and productive. Rather than pain relief, coloration, edema. So we felt that functional restoration would be the way to treat this condition. Chronic complex cases require prolonged treatment – up to two years – for these to get better. And one single technique of any kind has not been that helpful. Next . . . I'm talking about 93 patients we looked at consecutively, not double-blinded, but certainly prospectively, and in this our criteria were that we should have at least the majority of these patients with motor changes, so the motor changes have produced edema. And the majority of the patients, 80%, had triple-phase bone scan, and all of them had thermography. Slide shows temperature changes. Greater than 1 degree was considered significant. Functional evaluation was done in all. Range of motion was looked at in the affected joint, especially in the distal part of the extremity. Muscle strength and overall level of function of the affected extremity – e.g., leg, walking was considered. . . A person who had hand involved, it was buttoning or tieing a tie. We also did psychological evaluations, clinical interviews, and MMPI – not talking about here from the point of view of regional anesthesia – it was not there to relieve pain, it was there to restore the function. So if pain stopped the functional restoration, we would use the regional anesthesia – sympathetic block, lumbar sympathetic block (needle or catheter, etc). History of a 9-year-old girl who had a minor gymnastic injury to the knee following which she had a tremendous amount of pain and swelling and edema and motor changes in her extremity. She came to us 6 months later. She was not able to wait. So we did a diagnostic sympathetic block, after which we did a continuous infusion of the sympathetic, and it took about 2–3 months before she could walk without crutches and was completely better by 6 months. Next slide. This is a condition where sympathetic block did not work, and we went on to do somatic blocking, which we call an SIP. That sympathetic independent pain was controlled by a brachial plexus block. Which was confirmed by x-rays to see that the brachial plexus was adequately blocked. Next slide. The purpose of that was not pain relief but improve function. This person recovered completely.

Even for the leg, we found that the somatic blocks, for SIP and especially for removal of edema, have been very useful – a technique we developed a few years ago at Texas Tech. A catheter is placed on the sciatic nerve and maintained there for a period of time we feel it is helpful for functional restoration. Next. In our patients, by age, we found the majority were between 20 and 39 years old, but a considerable number, about 15% were under 20, and there was small group over age 60. We also found that at stage 1, 35% of patients, had increased vascularity, allodynia, etc. Stage 2, blotching, discoloration, coldness, edema and autonomic dysfunction. It was surprising for us to find that the sympathetic block was only helpful in about 22% of patients. They were SMP patients but they had to have a combination of sympathetic, intermittent as well as continuous infusion to maintain their function. Also, somatic single shots were of absolutely no use. We had to go to continuous somatic infusions to maintain the functional restoration, and in fact the majority of our patients had sympathetic blocks to start with and as they developed went into somatic combined, which suggested that SMP continued on to become SIP.

Next. We looked at the result of the treatment for physical functioning, the majority of our patients were somewhere in the region of 50% level of functioning. They increased at 3 weeks and 3 months, pretty close to fully functioning ... and were doing well at the end of the treatment. We also found that the range of motion increased significantly, and the muscle strength, surprisingly, which was much weaker when we first saw them, improved with PT to a high level close to normal. So there were three components of physical functioning. 1. Function. 2. Range of Motion 3. Muscle strength.

Next. Interestingly, we found that if we categorized patients – outcome 1 – patient, full functional; outcome 2, patients needed some assistance, crutches, cane, outcome 3 – not much change. We found that the patient early on, outcome 1 was much better, pretty close to the clinical stage. But in the later stage, outcome 1 decreased. Outcome 2 improved in every stage, and certainly in later stages where patients got better but still needed assistance. So, I want to say that the regional anesthesia is not meant for pain relief, but for functional restoration. And this could not be done if pain is present, edema, discoloration present, and there is mechanical or cold allodynia. It is in those situations that we find that continuous infusions have been helpful. They have decreased all those areas, facilitating early mobilization, increased distal limb vascularity, with nutritional improvement – and the goal of continuous infusion is to prolong the pain relief to provide these conditions which will help the patient.

Questions.

Q. SMP – some controversy – If you use your advanced monitoring how many SMP patients do you find in CRPS I?

A. We only look for CRPS I; 11 patients with SIP – in all of them we found SMP if we performed better monitoring and thoracic chain blocks – we prefer this over stellate blocks for diagnostic use. Independent from history – longer than one year history, we found about 70% SMP, and nearly 100% in the first year.

Q. Is immobilization a good thing?

A. I agree that functional restoration (other than an athlete) towards normal, vascularity improves, minimalization of calcium deposition improves, and their functional range of motion, esp of metacarpal phallangeal and interphallangeal joints improves, which when swollen are very painful. Functional restoration is important at every stage – early or late.

Q. Immobilization issue again... Is there any early marker that would predict?

A. If you see patients early there is no need for them to have these procedures – we see them about 3 months later. There is dysfunction, swelling, osteoporosis, etc. In those circumstances, any movement is extremely painful and they went from SMP to SIP. It is in those patients where we have to do something where this continuous long-term pain relief is important irrespective of what technique you use. So if the patient could have functional restoration without pain we would of course do this. The other options would be systemic narcotic – but they haven't worked that well. At the most the intensity relief is about 60%, whereas in regional or continuous blocks, they are about 85–90%.

Q. Dogma – in treatment approaches. No certainly about early immobilization, etc. Many of my patients have undergone "torture" in terms of clinicians with good intents trying to restore function. I agree with getting a handle on pain problem ... mobilization ultimate outcome, but pain control is important. And I am concerned about staging. I'm not sure we understand staging enough to be dogmatic about it.

A. Voices disagree here – speaker says they wait till the patient can be treated by physiotherapy without blocks – suggesting that regional anesthesia increases the pain.

6. Use of peripheral nerve stimulation in the treatment of CRPS II

G. Racz

Lubbock, TX, USA

Comment about history – defining CRPS – treatment recommendations, etc., 4 or 5 years ago. I'm surprised I haven't sent the slide so far. Early treatment does not guarantee success, and late treatment doesn't mean failure. By far the commonest in our practice is to have some SMP and enormous amounts of SIP. If you only concentrate on one treatment modality, there will be havoc. You try everything, and when everything fails, you consider the more advanced modalities, e.g., neurostimulation, peripheral nerve stimulation for mononeuropathies, spinal cord stimulation for more than one nerve involved, and now we are getting into the realm of spinal narcotics and other drugs we don't even know about. I listened with interest to Marshall Devor showing that spontaneous firing of the DRG can be suppressed by systemic lidocaine in the rat. It's a very tempting, simple idea – people were running in subcutaneous lidocaine for severe RSD because of that work, but it doesn't work. But the concept does work. Sometimes, in patients we may have to milk it and modify it.

I am delighted to work with Chris Rerige. We think very similarly. We performed a long-term brachioplexus infusion for a man who had a metal spike through the median nerve. He would hold his hand in a fixed position – and the brachial plexus infusion would stop his pain completely. We take M. Devor's idea, but were more specific. We delivered the lidocaine on the nerve that was conducting the pain. We tried to get to the nerve, and if you put the arm in this position you can precisely map out placing a catheter. The ulnar nerve is close to the humerus, median nerve is in the middle, and the radial nerve is behind. So no sense putting a dilute, low infusion on the working nerve, because you may get the same kind of response when you are more lesion-specific. So we get the blood level with suppression of the ganglion and stop the pain so we can have the patient with a severe neuropathic pain and SMP work very well and open and close – it works well until you stop the infusion. We need other treatment modalities. CRPS has a number of components, neuropathic, sympathetic-mediated, psychological, motor dysfunction, autonomic changes. We need to look at a number of them, and the neuropathic pain in CRPS is a very important aspect. I was lucky enough to be invited by the American Society of Neurosurgeons and met Dr. Bill Sweet – they stimulated intraorbital nerves – their own – found if you set the voltage just right you can get a sensation of fine tingle. That in turn led to changing a perception or sensation in a peripheral nerve. Wepsic, a young neurosurgeon working with Bill Sweet, had the notion of putting a cuff-like electrode around the injured nerve and the severe neuropathic pain, the "touch me not" pain, would be converted to a sensation of fine tingle, merely by applying stimulation to the peripheral nerve. Now this particular form of controlling causalgic pain worked for a while but it lost significance because scarring ensued and the Bennett model created pain and yet we were stuck with these patients, with nothing more to offer. Then we thought if you could stimulate the spinal cord through the dura perhaps you can stimluate the nerve also through a protective layer of the patient's own tissue. It's interesting we came to this notion about the same time as Bill Cooney at Mayo who was doing it with other neuropathic pain so we started doing this for RSD or CRPS type pain. Harvesting a piece of fascia, and then covering the electrode with a piece of fascia and then stitching it beneath the injured nerve where the pain is coming from. We've done about 300 of these now, and so for sole of foot pain, tibial nerve, top of foot, ulnar, radial, above the elbow, upper extremity . . . etc. so the candidates we've been looking for – patients with indirect nerve trauma and CRPS II when we know what nerve it is. We have a few patients with postherpetic neuritis, also, who have done well. Girl with ankle injury that affected whole half of her body – she was recipient of Devor's idea of subcutaneous lidocain infusion. I'm convinced that it might work on a single DRG, but maybe not in patients. We've been looking at this peripheral nerve stimulation with one of my colleagues, Jim Heavner, a neurophysiologist, who I was able to convince to look at this patient with an electrode underneath median nerve in a patient with severe painful median nerve neuropathy and he was able to get a recording of spontaneous firing. We believe that the nerve changes function, that instead of just conducting impulses it generates impulses, and this is the pain. If you move the extremity the firing does increase – more pain. M. Devor does have some recordings from DRG from single cell from A fibers and C fibers and they show that there is spontaneous firing that is going on at the DRG and they feel that you could probably record from the peripheral nerve as well. So some changes are taking place. When we do peripheral nerve stimulation we deliver a square wave

pattern at a different rate – that stimulation is perceived as a fine tingle. That kind of activity can be spontaneous or aggravated pain when you do more physical therapy and exercise. This is more activity when you do more physical therapy. Question of amputation – I am opposed to it. Residual problems of amputation – phantom pain, "touch me not" pain, etc. Not an option. We explored this amputation stump pain by exploring the sciatic nerve and placed a peripheral nerve stimulator implant on the sciatic nerve, because it was an ankle pain, and as soon as the patient wakes up, you turn the stimulation and you can touch it – it is that quick, almost like black magic.

We are substituting that spontaneous firing with square wave pattern stimulation which does work in this kind of pain. Six weeks later this person is able to wear clothes – she still had some central pain, we tried spinal cord stimulation and spinal narcotics – this patient elected to use spinal narcotics. Some patients do well, others have peripheral edema, etc. Then we tried spinal clonidine, etc. Recent evolution of peripheral nerve stimulation where we put the electrodes in a concave paddle where we can stimulate longitudinally and across because the nerve lays in a groove. Under anesthesia, we can put a tetanic stimulus – positive/negative, an excessive stimulus so that the nerve bundles have sensory motor fibers so you can provoke a motor contracture of the foot when you are stimulating and you can rotate selectively so you can have a tibialis stimulation and plantar flexion and dorsiflexion when you are along the bundles, which is mainly the peroneal fibers. So that has been a useful evolution in peripheral nerve stimulation. It is interesting how the nerve looks when you have a leg that is straightened out – it is as tight as a piano wire. Now when you flex the leg it's also surprising that the nerve becomes like a snake; if you make it tight at first more and causes more pain. It is not surprising that one of our problems is to prevent the patient from keeping the joint in a flexed position. Once you lose the joint that is the biggest battle to regain the joint function – not just to stop the pain. Our biggest cooperation with PT is prevention and regaining of joint function. So this is one of the areas. As far as peripheral nerve stimulation it has been accepted by the consensus group of the Am Soc of Neurosurgeons for mononeuropathy. But when you have more than one nerve involved it is not recommended – you tend to go with spinal stimulation, narcotics or other options.

What about outcome? We looked back on five-year follow up and the good to excellent pain relief in a subgroup of patients, worst of all, men and women – 70% good results – with 54% of men going back to work; 32% of women. And the happiness rating in this miserable group of patients is in the 80% range. Our results have been reproduced by Michael Stanton-Hicks and Sam Hasenbush, and it's been published, and their results are similar. Spinal cord stimulation in the midline by itself doesn't work – a man in car accident, with massive swelling – did not reverse the pain. So we have to go back, SMP, SIP, sympathetic block, infusion and then have an entry zone stimulation with double electrodes closer to the side that you map out that the information is coming in, or you go after the nerve root from where the worst pain is coming. In four or five days this same person, the swelling is down by going after the sympathetic and neuropathic component of the pain, so that the system that came after the consensus group works, there is wisdom putting clinicians and basic scientists together.

In order to look at the issue of peripheral nerve stimulation and spinal cord stimulation we combined our series from Baylor group – and it is quite interesting that the visual and analog pain score up to 36 months, spinal cord stimulation works, it gets the pain down dramatically but is not as good as peripheral nerve stimulation, and the best long-term results for 36 months were when you had s cord stim and periph nerve stim as well. So I believe there's a central component of the pain – sympathetic and neuropathic – and in combination we have physical therapy and psychotherapy as well.

7. Use of clonidine in CRPS

R. Rauck

Winston-Salem, NC, USA

Slide: Different ways clonidine can be administered. It's not just an epidural or intrathecal agent. I've used it orally, but haven't had as much success using it orally in CRPS, though I must say in some patients with cold allodynia or temperature instability, the oral route will help sometimes. Transdermally, in the US available only in a patch, and again in areas of very discrete hyperalgesia and in experimental models as well we've seen success with transdermal applications. I've been part of a phase 3 trial where clonidine was delivered in a gel in a nice double-blind, placebo-controlled fashion, and again it looks like it may be effective in that situation with mechanical allodynia and hyperalgesic states.

There were some protocol problems and a placebo response, but certainly these other types may have a real role in CRPS patients when we look at clonidine there's an alpha 2 predominantly and some alpha 1 activity. Most of our work has been with epidurals – we've looked at it in bolus forms, from 150 to 900 microgram bolus doses, and infusion rates predominantly in 20-50 microgram infusions. We haven't known the dose equivalencies between epidural an subarachnoid routes, though Jim Eisenach is getting ready to publish some work that has looked at some of that in human volunteers. Our clinical data has suggested that these are probably higher doses and this is what we used to use, an we now back down to a lot of our patients where we start at about 4–8 microgram per hour subarachnoid doses. But at least in patients it hasn't been looked at.

We looked at chronic, nonmalignant applications – it's not just for CRPS – it has been used in spinal cord injury, a small series have looked at it in postherpetic neuralgia. Stuart DuPen is using it quite frequently there. We've used it as well in diabetic neuropathy, and I'm willing to address the visceral pain which has also been looked at. Two very quick studies that look at this drug in animal models – Dr. Fuchs work in 1991 that looked at it in a rat model of a sciatic nerve lesion, with clonidine vs. saline controls and found a significant decrease in autotomy in rats that got the intrathecal dose – so it was impressive at least in reducing that type of neuropathic pain response. And following up on that we looked at Wang's work with clonidine and its effect on spontaneous sympathetic activity and afferent A delta and C fiber somatosympathetic reflexes in dogs.

Now, trying to look at some of these things in the basic science work. This looked at spontaneous sympathetic outflow and afferent a-delta and C fiber somatosympathetic responses and these were depressed with clonidine, whether it was given epidurally or intravenously, and there was a ratio of 1 to 4. So clonidine did seem to have a local effect that was four times more potent than IV routes of administration in the animal model when looking at both spontaneous sympathetic outflow and effects on afferent Adelta and C fiber responses. The intrathecal clonidine also inhibited both local sympathetic outflow and peripheral sympathetic effects. It wasn't clear mechanistically how it was working in that fashion. Interestingly, in this animal model at least, it was different from what Jim Eisenach and ourselves and others have looked at and felt and in this paper intrathecal clonidine did not seem to affect the descending inhibitory efferent pathway. Spinal clonidine, similar to either local anesthetics or other agents, did have a direct action on intrinsic neurons in the spinal cord. So this is data we looked at in patients with Reflex Sympathetic Dystrophy and our work with epidural clonidine. These were some of the severe patients in our group. A man with trivial injury who developed CRPS, and had severe Pseudomonas infection – allowed clonidine but no physiotherapy, healed up lesion, got rid of a lot of swelling, but he developed an epidural abscess from catheter, and lost his leg, has same kind of pain. Man 2, one of few – saw early – smashed ring finger – unfortunately watched this patient has not done well, progressed disease despite blocks, etc., did not respond to clonidine.

Put a catheter in and gave either normal saline or two doses of clonidine in phase 1, and if they responded to clonidine but not to the placebo we allowed them into an open label phase, which was a continuous infusion that went on with temporary catheters. Different from data in cancer patients. One – we saw a low placebo response, about 10%; did not see dose response, at least with 2 responses. Follow up , classic for pain patients – thought it was best they'd received. Again, when treatment was stopped pain tended to recur – but did not reverse natural history.

Some issue about rates – looking at epidural vs. oral – double – blind fashion. RSD patients. Cold sensitivity testing, where we subject patients to stresses with a refrigerator type apparatus and looked at laser Doppler flow and vital capillography, which allows us to look at capillary blood flow through the nail beds.

Slide. We put thermistors on each of their digits and then in the cool environment for 20 minutes, then re-warmed, and in patients with CRPS, this being laser Doppler flow and flux that you measure you see an inordinate amount of spiking which is not normal. As far as total flow it can vary from one to another-some have better flow than others, but we do tend to see this spiking. Before and after – difference after clonidine. Damping with clonidine, epidurally, vasomotor stability.

In our orthopedic lab, we know there's a lot of alpha 2 receptors at the arteriovenous shunt that occur is the distal extremities. So it seems that this shunting allows for inappropriate opening and shutting and microcirculatory changes in the periphery at this level. I think the clonidine, maybe through a central mechanism, or a peripheral mechanism, possibly through both, is affecting this type of flow pattern in patients where the shunting is not done well.

Side effects. . . Epi or spinal – have to worry some about hypotension, but we're comfortable enough to

use it as an outpatient drug. By bolus, larger doses even better tolerated – but sedation. Hypotension worry more if you're giving it in the higher thoracic region-T1 through T4. Cervically and lumbar it's well tolerated. Sedation, you have to worry, and you can see some mouth ulcers that are not herpetic in origin.

To summarize in CRPS. . . Now, we have used clonidine in some early CRPS – effective, but is it more effective than spinal cord stim, physiotherapy, conservative treatments? I don't know, but I can tell you that it helps. In the recalcitrant patients, with short term applications, there is some limited value. Most in my experience, the disease process returns – unless you can significantly improve function and get them to maintain functional improvement . . . what we classically do clinically is we put in a temporary catheter, send them to physiotherapy and monitor for a week to ten days and if their therapist tells us that they are performing functional improvement, pain relief, better. We resurrected the use of the DuPen Catheter – that exteriorized catheter, and we put it in for use for three to four months. I do have two or three with them in for over two years and have done well. If it works but then gets dislodged, etc we can convert it to an intrathecal pump. We don't run it with any opiates – I don't have good data. The reason we use this therapy is because these people want to get back to their lives, professions, etc.

8. Neurostimulation in CRPS

M. Stanton-Hicks

Cleveland, OH, USA

Slide. I'd like to discuss two things. One is the algorithm generated at the Malibu workshop. A disclaimer. An attempt to try and order the type of treatment that can be used. The algorithm was intended, not to prioritize treatment but to indicate those modalities and treatments that can be used. The principle of the treatment algorithm is a physiotherapeutic restoration of function, and any of those things discussed today are adjuncts for that purpose. While the methodology of, and manner in which physical therapeutic measures are introduced is debated, the whole idea of trying to improve function and restore this in patients relies very much on being able to deal with the patient's depression, pain, sympathetic component if this is present, and the psychological aspects that accrue as part of the disability. So as clinicians we have three things to do: Control pain to allow rehabilitation process to take place; this would be much better in hand if we knew the mechanism of the disease – we could turn off the disturbance, sympathetically maintained, sympathetically independent pain.

Neurostimulation – We are discussing spinal cord stimulation as opposed to peripheral nerve stimulation. The basis of this depends on things that began almost 34 years ago when White, Melzak and Wall were working together in Boston, and with Sheeley, found that you could interfere, or confuse, the type of nociception, or pain that the patient felt. The theories of spinal cord stimulation are still in the sky. We do not know how the methodology works. It was thought that it could be simple by just altering the balance between large and small fibers as in the gate control hypothesis, but now it looks more like there is a stimulation-induced change in both inhibitory neurotransmitters and also some block of excitatory transmitters.

Slide. The rationale for neurostimlualtion is that we're dealing with a neurologic disease. One of the interesting facts about spinal cord stim or periph nerve stim is that it has very little effect on nociceptic type pain, other than vasculopathic pain. It induces sympatholysis and when this is introduced in the patient with CRPS or mononeuropathy there is an instant improvement in the microcirculation with increased warming and after some weeks the circulation resembles that on the opposite side. Analgesia is produced in those cases in which it works, which suggests that there must be a trial, a test period, before one puts in a very expensive piece of equipment. And it does have motor effects – something I've observed over the past 11 years Some patients with peripheral nerve stimulation begin to exhibit, in their 7th to 8th years, an interference with the antagonist or agonist muscles, e.g., in the foot, and they develop a plantar flexion, and when the stimulator is turned off for a period the foot will go back into a neutral position. This may require changing the electrode position and reapplying the electrode. So there may be some motor effects that occur, certainly the window of treatment in peripheral nerve stimulation, compared to spinal cord stimulation, is much narrower. One does not have the large difference in stimulation amplitude affecting sensory fibers and motor fibers. It is effective, it seems, in CRPS I – the situation is of a global nature so spinal cord stim is more appropriate than peripheral nerve stimulation for a disease that affects an entire region – not a distribution of a single nerve. The stimulation has more effect on the longitudinal or dorsal column, as opposed to the dorsal root, which is one of

the problems in determining what stimulation parameters will be most effective. So there is a ratio that is determined during the application when one is trying to achieve paresthesias that will affect the region. Multiple electrode contacts are better than one. During the trial one finds vasodilatation, and of course improvement of the microcirculation. Slide. The problems that occur with spinal cord stimulation, unless the electrode is placed via laminotomy or laminectomy – in which case the electrode, paddle type, can actually be sutured to the dura. Where it's placed percutaneously depends on the anatomic arrangement of the epidural space and in some patients it may be quite unsatisfactory because the electrode moves around. There may be no relief, and the stimulation may not be tolerated. Some are unable to stand the tingling sensation. This is in spite of the fact that all of these patients have to undergo a psychological assessment to make sure they will be compatible with implantable technology; it may be that those patients who are intolerant of the stimulus were not adequately assessed psychologically. We're using a technology in a biological environment so there can be breakage and other failures. Patients are accepted after they have failed all other treatment modalities for their condition. Therefore, it requires an interdisciplinary approach – that's the only was these patients can enter this realm of treatment, in which they have failed to progress and meet the criteria for neuromodulation psychologically and as a result of a successful trial. One makes the decision at that point whether to use spinal cord or peripheral nerve stimulation. Treatment failures for implantable therapies in most cases are attributable to suboptimal patient selection. The type of test that we use, McGill pain questionnaire – and if we're looking at this from the point of view of outcome studies, add the Oswestry disability (although designed for back pain it is still useful in these patients). Now I will go over some of the literature that supports the use of spinal cord stimulation – mostly anecdotal, not prospective, randomized controlled studies – but the only things available over the years. In 1986, this group found that in 11 patients, 8 of these had about 75%. You find that this satisfactory figure of success comes all the way through. Next. 18 patients, with four receiving no relief during the trial who were rejected, and 75% of the remainder had good to moderate relief. Three stopped and three reduced their narcotic use. This is a pattern we found in the paper that we published on peripheral nerve stimulation.

Next slide; 24 total patients, 11 with CRPS. At 36 month follow up half had some symptom improvement, and 89% had overall excellent result, but we don't know what that means.

Next. Another group, 8 patients with upper extremity pain. Follow up was 36-months, 7 with good to excellent relief, one with fair relief.

Next. And from Canada; they have collected a large number of patients over the years. Thirty of their series had CRPS; 40-month follow up. All had good to excellent pain relief, with 2 patients using occasional narcotics. This has been our experience among all of us who have used this modality.

Next. Six patients from Pittsburgh, CRPS, all with very good relief. They tested the resting sweat output as well as the quantitative sudomotor reflex test (Mayo method) and values are either improved or normalized, and they now have a prospective study.

To conclude. This is a modality usually introduced late in the course of this disease when other treatments have failed. Some (especially the Japanese) have used this techniques as a first line approach in children (exteriorized electrode); good experience in combating the problem of trying to restore function. We believe this a useful tool in both CRPS I and II, used after failed conservative treatments and after regional anesthesia has normalized things (anesthesia can't be used indefinitely). We believe, based on studies from Uppsala and Stockholm that there may be some change in the coupling between the postganglionic sympathetic fibers and the primary afferents as a result of the stimulation, that there is a reduction in the adaptive SIP sensitivity and that overall it has become a very useful treatment modality.

9. Primary afferent mechanisms of neuropathic pain

M. Koltzenburg

Wurzburg, Germany

I will focus on mechanisms involved in the variety of pain syndromes studied in patients with sympathetically maintained pain, neuropathic pain or inflammatory pain. I want to show some commonalities and differences.

Slide: Patients with sympathetically maintained pain, or CRPS, are enigmatic – we still don't know the mechanisms underlying it. For this purpose it's important to study, on a descriptive level, the symptoms that these patients have because these give us clues about the

underlying neurobiological basis of the disease. This is important not only for clinical purposes, but also for giving us a clue to animal models. These studies in humans will help us to find targets that are important for the development of neuroanalgesic drugs.

Slide: Patients are diverse. Looking at those posttraumatic neuralgia patients with demonstrable nerve lesions, it's clear that there are two components of their pain. One is a stimulus-independent pain. The others are stimulus-induced pain – hyperalgesias – and one of the prominent features in these patients is not only hypersensitivity to mechanical stimuli, but also to thermal stimuli. Now, it is still unclear why the divergence of thermal hyperalgesia develops in patients. This is from a study years ago looking at a subpopulation of patients in which we looked at the thermal thresholds of patients presenting with posttraumatic neuralgia. These are the readings from quantitative sensory testing of QST, where the blue shows the normal uninjured side, and red the symptomatic side. What you can see is a group that can be identified having heat and cold hyperalgesia – there's always a significant difference of several degrees centigrade between the thresholds on the affected and unaffected sides. These patients also have good warm-cold differences, suggesting that the small fibers in these components are presumably well preserved. Two other groups. One that is probably the most prevalent population of patients with posttraumatic neuralgia – those presenting with only cold hyperalgesia. The heat pain thresholds are identical – only a strong difference between affected and unaffected sides with respect to cold perception. In this group there is also a significant difference in the cold-warm detection, suggesting that there is a severance of A Delta and C fibers. Then there's a group with no thermal hyperalgesia.

It is still unclear whether there is only one underlying mechanism in these symptoms. I would suggest that this is incorrect and that we can dissect some of the mechanisms that underlie these hyperalgesias in patients using very simple bedside tests.

It's clear that following either peripheral nerve lesion or chronic inflammatory tissue damage we have changes in the peripheral and central nervous systems. The nociceptors will be sensitized. Neurons in the dorsal horn of the spinal cord and presumably at higher brain centers are also sensitized.

In the past, it has been customary to divide central and peripheral mechanisms and find where the main generator of the pain is. I think it's more appropriate to see different symptoms as modular systems that can coexist perhaps in different patients, and that each symptom in itself is mediated by the skin, peripheral and central pathway and changes therefrom.

I think it's often forgotten that there are some very simple basic clinical observations that yield information about the underlying pathophysiology of the disease. And we must not forget that these data are not coming from large studies, but most of you would agree with the following statements. Local anesthetic blocks of inflammatory tissue and affected nerves often completely abolish the pain. It seems like a truism, but people forget the simple fact, namely, that the main cause of any chronic neuropathic pain or inflammatory pain, for instance, comes from the periphery.

Moreover, differential block of large, myelinated non-nociceptor fibers usually does not eliminate ongoing stimulus-independent pain. This means that if you can abolish the pain through a complete block, at least the pain unaffected by the block of non-nociceptor fibers, it's only the nociceptor fibers that can carry nociceptive input. And furthermore many forms of stimulus-induced pain, many forms of hyperalgesia, persist during a differential nerve block, indicating also sensitized C fibers, and nociceptors, that are presumably playing an important part.

Let's see how changes in primary afferent neurons convey this. It is useful to differentiate between different types of pain. Hyperalgesia is not monolithic, it is extremely diverse, complicated, and when we just look at those mechanisms that have been discovered in humans, we can see that it's very easy to differentiate between mechanical, thermal and chemical hyperalgesia, but it's also possible within each modality, to subdivide the different types of hyperalgesia. I will show you evidence that they are indeed distinct. We have mechanical hypersensitivity to brushing stimuli, to pin prick, to pressure, and to impact stimuli. There are very distinct symptoms, and it is often possible to define and dissect some of these in humans. Thermal hyperalgesia to cold and heat are presumably very different as well.

Studies come from patients and from human surrogate models, where we've been able to dissect many of the underlying mechanisms and then compare them with the conditions we find in humans.

Summary slide: some of our work where we looked at some of the mechanisms that on a descriptive level have been observed in humans following an experimental injury – freeze, burn, etc. Two types of hyperalgesia. – primary hyperalgesia refers to the zone with direct tissue damage; secondary hyperalgesia to the zone where there's seemingly no tissue damage but where there are

sensory abnormalities. Primary hyperalgesia is mainly carried by sensitized nociceptive C fibers. This holds true for the majority of hyperalgesias. Secondary hyperalgesia is a function of a sensitized CNS – not to say it is entirely CNS correlated, but there are also peripheral aspects to it. It is carried by very different subsets of primary afferent neurons, no nociceptor fibers are involved in mediating brush evoked or pin prick hyperalgesia; it is presumably mediated by A Delta fibers. These two are very distinct as seen in patients.

It is quite clear that the acute pain with which we usually deal, does not involve any major form of sensitization. Needle procedures commonly carried out in the clinic will involve activation of nociceptor, activation of secondary spinal cord neurons, and a perception of pain. There's no sensitization here.

What happens following mild tissue damage? It's now becoming clear that the neurophysiological correlate of heat hyperalgesia is the sensitization of peripheral nociceptors. With microneurography in human volunteers we recorded from the superficial radial nerve and you can see here that this unit had a receptive field at the base of the third finger. It responded with a very long latency to electrical stimulation in the receptive field, indicating that it's a C fiber. Now, here we plot the discharge of this particular C fiber to a standard heat stimulus that went up to noxious levels, and each of these dots represents one action potential – you can see that at a certain intensity of the stimulus there's a discharge – at this point the subject told us to switch off the stimulus because it was too painful. You can see that following mechanical irritation at that point the mechanical stress produced reddening of the skin and presumably some form of minor inflammation. There was a dramatic change of the stimulus response function – the unit started to discharge much earlier to the same stimulus, the discharge was much higher, and the peak frequency was increased. This is the neurophysiological correlate of heat hyperalgesia which has been known for a long time.

Heat hyperalgesia, the basis for which is nociceptor sensitization, involves primarily C fibers in the hairy skin of primates, but in glabrous skin is primarily carried by sensitized A delta fibers (though there may be a C fiber component as well).

The sensitization to heat is not the only way a primary nociceptor in humans can change in response to tissue injury. Here is an example from the work of Torebjörk et al. using microneurography, where they mapped the receptor field of C nociceptors. What they showed is that the receptive fields of nociceptors in humans are very dynamic and plastic, and can change. Here you see that the receptive field is outlined in white, and the electrically defined receptive field where terminal branches are, is only a portion of that mechanically sensitive field. See what happens when you apply a chemical stimulus that sensitizes nociceptors. In this case the pungent ingredient capsacin. Here you can see that following its application (where you get mechanical hyperalgesia) there's a dramatic expansion of the receptive field that covers the extent of the receptive field as well as the part that has been treated with capsacin. The functional consequences of this expansion in the periphery is quite simple – imagine that if you have a stimulus that will cover this part it will now result in a spatial summation in CNS synapses, more active units will be discharging following sensitization in response to a given stimulus. This again is another mechanism by which peripheral nociceptors could contribute to an increase in excitability after inflammation.

Results from Wortzberg's work show a dramatic example where you can see the recruitment of so called sleeping nociceptors (mechanically insensitive nociceptors) that are only activated during inflammation. In the control condition, flexion of knee joint and manipulation did not produce anything, but following inflammation we can see a nice activation of these so called sleeping nociceptors.

In aggregate we have several mechanisms that could contribute to sensitization of nociceptors in the periphery. One particular instance is the possibility that the sympathetic nervous system interacts with primary afferent neurons. We have heard from Häbler a remarkable specificity of the projection of the sympathetic neurons to different target tissues, so can there be an interaction following pathological conditions? The consensus is that following a peripheral nerve injury there is expression of alpha adrenoreceptors at the site in a peripheral nerve lesion. This is either at the neuroma site or even distal to a partial nerve lesion in the seemingly uninjured nociceptors of the skin. There is also evidence now that there's an expression of alpha adrenoreceptors in the cell bodies that may be functional.

Work from the Hopkins group showing why there is a sympathetic component in patients with sympathetically maintained pain – local anesthetic block of sympathetic ganglia, as well as infusion of phentolamine in a placebo-controlled fashion can reduce pain in a select group of patients. In CRPS it is possible with this kind of stimulus to find different populations of patients in response to their sympatholytic therapy.

I will briefly summarize the mechanisms that are thought to underlie this coupling between primary afferent neurons and sympathetic neurons. This work we did in Torebjörk's lab. Some of the patients with sympathetically maintained pain respond to a challenge of noradrenalin with an increased pain perception. Here's a patient, following injection of noradrenalin, who showed an increase in pain and a remarkable expansion of the response to mechanical brush-evoked stimuli. We know from differential nerve block experiments as well as in combination with local anesthetics that the fibers that are responsible for mediating this noradrenalin-induced pain are presumably C fiber nociceptors.

Work from our group on an animal model with partial nerve lesion shows that some of these C fiber nociceptors that respond, and project into a peripheral nerve also acquire spontaneous activity. This is very unusual under normal circumstances but you can see that under pathological conditions there is ongoing discharge. In this particular instance we could show that after partial nerve lesion the spontaneous activity arose from seemingly uninjured neurons in the periphery because after using a local anesthetic block at the peripheral site you could see complete abolition of spontaneous activity in this condition.

This is work Häbler and I did a long time ago, showing that catecholamines are capable, under certain conditions, of exciting nociceptors. You can see a recording from primary afferent neuron here, and stimulating the sympathetic neurons in this region excites the afferent neuron; this excitation and pathological coupling between sympathetic neuron and primary afferent neuron is entirely abolished by the administration of the nonspecific adrenoreceptor block by phentolamine, indicating that it's mediated by alpha receptors.

Here is some work showing similar findings; that the application of noradrenaline to the receptive field of the nociceptor results in the excitation of this nociceptor. This work has also been reported by the Hopkins group in primates showing essentially the same findings; in partial nerve lesions, the remaining nociceptors have the ability to become responsive to catecholamines.

This slide summarizes some of the change in the periphery. I told you that ongoing pain, or so called spontaneous activity of primary nociceptive neurons, eg, hyperalgesia carried by sensitized C fibers. Three mechanisms have been identified and can be broadly shown. We have hyperalgesia, sensitization of primary nociceptors, the cellular mechanisms become more and more understood. McNorton in Prague showed that sensitization to heat is presumably mediated by an isoform of protein kinase C epsilon. The expansion of the receptive fields is also an enigmatic finding – we still do not know what the mechanisms are. Presumably, there is some involvement of chemicals, because this could be induced by the pungent ingredient, capsaicin, which acts on the substance P receptor. The recruitment of silent nociceptors is a key to our understanding of some of these pain states. Torebjörk now thinks they have data showing there's a subgroup of primary sensory neurons capable not only of signaling some inflammatory pain, but of signaling some mechanical algesias, and appear to be particularly important for mechanisms involved in central sensitization.

10. Central mechanisms of pathophysiological pain

D. Price

Gainesville, FL, USA

This is an account of the relationship between peripheral/neural input and central mechanisms. Two types of studies. 1. Human neuropathic pain studies done at the Medical College of Virginia by Bennett, Raffi and Long; and 2. Hyperalgesia and morphine tolerant studies done by Mao and Mayer.

Three hundred patients were given nerve blocks at University of Virginia for CRPS I or II, and the vast majority get strong and at least temporary relief of their pain. In a pilot study of 40 patients, over 90% got relief from block of a peripheral nerve of some kind. The problem of nerve block is that the area gets numb, and the patient knows that a local anesthetic has been given. It is therefore difficult to do a double-blind study. The advantage of sympathetic block is if you do it well, the area does not get numb and the patient cannot objectively distinguish between saline injection into the sympathetic ganglia vs. lidocaine or other anesthetic. This is a description of a crossover study in seven CRPS I patients in which one week they received saline injected into the sympathetic ganglia and the other week they got lidocaine or lidocaine with bupivacaine injected into sympathetic ganglia. The order of administration was randomized across paitents, and was double-blind. The point here is that the initial effect of saline is not statistically different from that of lidocaine. Both cause very strong reductions in pain – the difference is in the duration, and that is what distinguishes lidocaine

from saline. One might interpret this as being a reliable test of sympathetically maintained pain. I would NOT make this interpretation, however, because the time at which the unique contribution of lidocaine is evident is at a time after the sympathetic block has recovered on days 3, 4 and 5. So the result may not be exclusively due to sympathetic block. It may due to a stabilization of ectopic foci or abnormal sodium channels of damaged peripheral nerves or at least small branches of peripheral nerves. What this does show, though, is that there is a peripheral generator to these patients' pain, the extent to which this generator is maintained by sympathetic efferent activity or ectopic foci or abnormal sodium channels is not entirely clear.

To elaborate on the idea that sympathetic blocks really cannot tell you whether the pain is sympathetically maintained or not, data from a single patient under ideal conditions show that saline injection produced a very profound drop in pain. This was a very stable natural history, and the lidocaine infusion clearly produced a much longer duration, again long after the sympathetic block had recovered.

Frequently, when a patient has a very unstable natural history, with pain fluctuating, it is very difficult to determine whether saline or lidocaine is having any effect. I would say that individual sympathetic blocks make it very difficult under many circumstances to determine whether the pain is sympathetically maintained or not. Nevertheless it does show that there is a peripheral generator of activity.

The following is an account that suggests that the CNS is involved in CRPS. This is an experiment from 1989 showing that stimulation of A beta axons at regular intervals, one every three seconds, produces a temporal summation of burning pain. We showed this in two ways. By dragging a cotton gauze 5 cm across the pathological zone one can see that with one in every three seconds stimulation there is a gradual build up of intense, burning pain. This can be made to go away by injecting lidocaine into the stellate ganglion. After complete block you can see that this temporal summation disappears. This also occurs with electrical stimulation of the lowest electrical threshold axons in a nerve supplying the pathological zone, so transcutaneous electrical stimulation of A beta axons also produces temporal summation. It can be blocked by lidocaine injected into the stellate ganglion. In normal human beings, stimulation of A beta axons, even up to 1,000 Hz, will not cause pain, just a buzzing, tingling sensation but not burning pain. So the elicitation of burning pain by A beta axons is abnormal and suggests somewhat indirectly that the CNS must be involved in the production of these pathological pain states.

Now one general mechanism proposed to account for A beta allodynia, is that A beta axon input must somehow gain access to a mechanism that already exists in human beings, namely slow temporal summation. We know that slow temporal summation of pain can be induced in normal humans by stimulating their C fibers at one every three seconds – that's called windup. We know that this is mediated by N-methyl-D-aspartate (NMDA) receptors and the similarity between the temporal summation of A beta allodynia and that of C fiber pain suggests that this may be also an NMDA receptor mechanism. The A beta axon impulse input may somehow gain access to the same NMDA receptor mechanism that is normally triggered by C fiber input. One possible way that this might occur indirectly is by a breakdown of inhibitory mechanisms. Normally, A beta axon stimulation is what we use to inhibit pain. This is why nerve stimulation, transcutaneous nerve stimulation, and dorsal column stimulation are used to inhibit pain. This is a case of A beta allodynia which causes patients to say "my TEN stimulator does not work and produces the very pain I'm trying to escape from." The breakdown of inhibitory mechanisms seems to be apparent in some patients.

There is considerable diversity of sensory abnormalities among a group of 31 patients with CRPS I or II – all had ongoing pain, 17 had heat hyperalgesia, and all had some kind of mechanical allodynia. We broke down the mechanical allodynia into two types – A beta, which I have just described, and in which we verified stimulation of A beta axons by either mechanical or electrical means, produces burning or throbbing pain; and in the other which we call high threshold, ie, people who did not have A beta allodynia but who had allodynia to stronger mechanical stimuli that would not be perceived as painful in normal people, nor in the contralateral limb of CRPS patients. Of importance is that 10 of 27 patients had slow temporal summation of mechanical allodynia. We have heard much about stimulus-dependent and stimulus-independent components of pain. I would like to suggest that at least some component of ongoing pain in these patients may be stimulus-dependent. Seventeen CRPS patients without slow temporal summation of mechanical allodynia had an ongoing pain intensity of 4.04, whereas the 10 CRPS patients with slow temporal summation had an ongoing pain intensity of 7.02. The difference between these two ongoing pain intensities was significant at $P < 0.001$.

I believe that the slow temporal summation of A beta or higher threshold allodynia may be integrally related to what we think of as spontaneous, ongoing pain in patients. Listening to these patients tell you about the natural history of their pain during the course of the day tends to make sense. They say things like, "when I get up in the morning and put on my clothes it starts to hurt." "When I get up and walk around it hurts more – the more I move the more I touch the environment, the more it hurts, and it builds up slowly over the day." So that evoked pain and ongoing pain may have some component that is integrally related. However, this is not the whole story because patients without temporal summation do have an ongoing level of spontaneous pain.

Some animal studies have further elaborated potential mechanisms that may be involved in the pathophysiology of these disorders. Typically, one approach is to record from neurons in the dorsal horn using microelectrodes. Sometimes, "backfiring" these neurons from the thalamus, ie, spine, thalamic tract neurons, or simply recording from single units in the dorsal horn and determining their inputs to control stimuli under both normal and pathoophysiological conditions. If we look at the junction of the first synapse, we see that all kinds of primary afferent neurons converge on and symmetrically excite cells of origin of these ascending pain related pathways. This could very well be a spinothalamic tract neuron, e.g., a wide dynamic range neuron (WDR), which receives input from A-beta afferent, different kinds of A-delta nociceptors and from C nociceptors. As you can see, A beta input normally activates interneuronal inhibitory mechanisms, providing a balance between inhibition and facilitation in respect to the output of this neuron. C afferent input uniquely activates NMDA receptor mechanisms and produces facilitation. So this neuron responds over a very wide range of stimulus intensity, from gentle to noxious, and its output is determined by the balance of an inhibitory and a facilitory interaction as well as from descending control. When electrophysiologists record from these neurons the kinds of data they get are shown in the next example.

This is a response post-stimulus time histogram of a spino-thalamic tract neuron recorded in Willis's laboratory. One can see that with synchronous stimulation of all the axons in that nerve, and recording from a single spino-thalamic tract neuron, there is an early discharge and a late discharge attributable to the C fiber input. That is because this neuron receives a convergent input from all of these types of afferents. Now what is remarkable about the profile of this impulse discharge is that it looks like psychophysical judgments of human observers to similar kinds of stimuli. Synchronous electrical shock to the skin that activate A delta and C afferents produces a initial pricking pain followed by a dull diffuse burning pain, and this profile looks like that of second order neuron responses. Now interestingly, in the next slide you can see what happens to the second pain or to the C fiber evoked discharges when stimuli are repeated every 3-second intervals. This is from a dorsal horn single neuron recording of a WDR neuron, and one can see that with repeated stimulation at about once every second there is a gradual build up of the C fiber evoked discharge – i.e., the number of C evoked action potentials increases incrementally with each successive stimulus. This can be totally abolished by 5 mg/kg of ketamine, an NMDA receptor antagonist. An entire pharmacology of this kind of response has been developed – this is called "windup", and is thought to be integrally related to the production of central sensitization. Now what is interesting about wind up electrophysiologically is that it also occurs for second pain in normal human beings. These are psychophysically trained observers that were trained to notice and estimate the magnitude of response to second pain from trains of stimuli, e.g., like touching a hot stove every three seconds. They notice a first and second pain, and rate it accordingly. One can see that with one every 5 second stimulation there is no windup but with one every 3 second stimulation there is and all of this can occur after complete blockade of impulses in myelinated fibers, so it is a C fiber phenomenon. The second pain actually increases after blockade of impulses in myelinated axons.

Psychophysical studies of windup show that the windup of second pain is NMDA receptor mediated, a phenomenon very similar to electrophysiological experiments in wind up. In this study, we had subjects rate second pain in response to a train of heat impulses on the VAS. What we did on a double blind basis was give the vehicle, 15 mg, 30 mg, or 45 mg of oral dextromethoraphan, an NMDA receptor antagonist. The baseline ratings are shown as a solid line, and the dashes are the post drug ratings. You can see that the vehicle had absolutely no effect on temporal summation of second pain. There was a slight trend in the case of 15 mg but 30 mg, the standard antitussive dose, significantly attenuated wind up of second pain, and 45 mg of oral dextromethoraphan completely abolished the temporal summation of second pain. Wind up is integrally related to mechanisms of central sensitization.

Intracellular recording of cat sural nerve stimulation in which A and C fibers were activated every 3 seconds elicited not only an initial response to the A fibers but also a delayed postsynaptic potential that did not summate. But with one stimulus every 1.5 seconds you see that the C fiber response builds up incrementally with each successive stimulus such that by the end of this train of stimuli the membrane is partially depolarized. Normal resting potential is the dashed line – there is a partial depolarization. Even more clear after 1 stimulus/second stimulation, there is a gradual buildup of these C fiber related impulses. This is important because in a way this mimics what happens in pathophysiological pain states. What one has in pathological pain states is some kind of tonic input from C fibers. It may not be very high frequency – perhaps only 1 every 3 or 2 pulses/second – but the tonic input from large populations of C fibers produces a gradual build up of depolarization – this causes an expansion of receptive fields of second order neurons, increases their sensitivity to evoked stimuli, such as touch, heat, etc – possibly integrally related to allodynia or hyperalgesia. One of the interesting things is that once sensitization takes place it can be maintained by extremely low frequencies of C fiber input. A. Larson et al. recently published a study showing that when dorsal horn cells wind up in response to repeated C fiber stimulation, the sensitized state that is accompanied by wind up produces an expansion of the receptor fields of these neurons and hyperresponsiveness to other inputs. The study shows that once sensitization occurs a sensitized state can be maintained by impulse frequencies as low as 1 impulse every 10 seconds. So once sensitization occurs, even extremely low frequencies of peripheral tonic input can maintain the sensitized state.

Now, what is really needed is an animal model of CRPS II pain that could simulate the role of tonic afferent input in central sensitization and therefore mimic a pain state. This is the Bennett rat model. This rat has many signs and symptoms that are like those of causalgia or CRPS II. In this model, four ligatures are placed around the sciatic nerve, barely constricting the nerve in four places. What happens is that the animal displays guarding of the hind limb, spontaneous pain behaviors suggestive of spontaneous pain, thermal and mechanical allodynia and hyperalgesia – many different features indicative of neuropathic pain. This model has been studied extensively around the world.

I would like to show you a very simple experiment in which tonic afferent input and central mechanisms interact. Thermal hyperalgesia scores in the normal contralateral limb and the ipsilateral hind paw were measured. Intrathecal catheters also were implanted in the lumbar subarachnoid space. Various agents were injected on day 3 after nerve ligation. What you see in this figure is the saline group: 8 animals on day 3 were injected once with a small amount of intrathecal saline – yellow line shows the natural course of the development of thermal hyperalgesia. It shows a peak on day 3 and a plateau from day 7 to day 15. Bupivacaine group: On day 3 (blue) a small amount of bupivicaine, .25% was applied around the sciatic nerve that had been ligated. You can see that there is a precipitous drop in thermal hyperalgesia one day after the bupivicaine is given. This is similar to what we saw in the human study after sympathetic local anesthetic block – i.e., the bupivicaine is acting 24 hours after it is given, and even after day 5 there is a trend toward a partial reduction in thermal hyperalgesia. NMDA antagonist group: if 2.5 nanomoles of MK801, an NMDA receptor antagonist is given (Red), a similar drop occurred and recovered on the second day after injection (all of these are statistically significant). What is interesting is that when a combination of bupivicaine and MK801 were given together there is not only a precipitous drop 24 hours later but there continued to be significant decreases in thermal hyperalgesia 5 to 7 days afterwards. Basically what this demonstrates is that this pain condition may represent in part combination of tonic impulse input in central sensitization mechanisms.

A number of experiments are shown in this next figure. Some of the intracellular pathways and membrane receptor mechanisms for the central sensitization tonic input mechanism have been elucidated. In essence, this process commences with tonic input along C polymodal afferents and other nociceptors which cause a sustained release of glutamate or aspartate. These agents act on membrane receptors of second order neurons. These sites include NMDA, AMPA, canate, and metaprotopic receptors. These receptors in turn, through protein mechanisms and others, activate what is known as second messengers, such as diacylglycerol. When NMDA receptors are activated on a tonic basis there is an influx of calcium ions. Other cofactors are peptides like substance P, etc., one of the main roles of these second messengers is to induce a buildup of free calcium. Calcium has a pivotal role because it activates other cascades, e.g., nitric oxide pathway, protein kinases, etc., but the pivotal function of intracellular calcium is to activate an enzyme called protein kinase C (PKC), and it is becoming apparent that PKC has a pivotal role in many intracellular events,

particularly protein kinase C gamma, which is an isoform. Calcium activation of PKC occurs as a result of translocation of protein kinase C from the cytosol of the cell to the neuronal membrane. When PKC attaches to the neuronal membrane it phosphorylates these ion channels including those of the NMDA receptor. Then it releases a magnesium block of the NMDA receptor, allowing a greater conductance of this channel to calcium. The functional consequence of this is that this receptor becomes sensitized – any subsequent glutamate release will have a greater postsynaptic effect because of the increased conductance of the NMDA receptor on this membrane. So this is like a positive feedback loop where sustained tonic input from primary C afferents produces activation of second messengers, build up of cytosolic calcium, activation of PKC and then phosphorylation of these receptors and their sensitization. Other glutamate receptors also do similar kinds of things, functionally.

The next figure shows one type of evidence for this mechanism depicted as an assay of PKC. High levels are red; low, yellow; lower, blue, etc. A representative cross section of the spinal cord at L5 of a rat with a chronic constrictive injury of the sciatic nerve – "Bennett rat" – is shown. A sham-operated control, in which the contralateral leg is opened and the sciatic nerve exposed, but no ligatures were placed. Basal levels of PKC are seen elevated in the superficial part of the dorsal horn. However, in the rat with a chronic constrictive sciatic nerve injury and hyperalgesia, etc., there is a distinct elevation of PKC in the superficial lamina of the dorsal horn. The elevations in the CCI rats were significantly greater than that of the sham controls. Peak elevation occurred on day 3. This next is a rat that has a chronic constrictive injury of the sciatic nerve, treated with an agent that blocks activation of PKC – GM1 gangliocide – and this rat has lower levels of PKC as compared with a similar, untreated rat. Not only was the level of PKC lower in this animal but the rat's behavior, the spontaneous pain and hyperalgesias, were also attenuated. This is based on group data and group statistics.

This last figure shows that there is an overlap of mechanisms of central sensitization involving PKC and mechanisms of opium tolerance so that there is a commonality of mechanisms of tolerance to morphine and central sensitization as a result of nerve injury. I've already described this pathway – a positive feedback loop. But it is also important to recognize that continuous occupation of the Mu receptor by morphine also is known to activate PKC. PKC can be activated in two ways – either by tonic glutamate input and calcium release or by chronic occupation of the Mu receptor. PKC that is activated then feeds back on the Mu receptor and causes its desensitization, i.e., an integral component of what we know as morphine tolerance can occur by this negative feedback mechanism. It can also occur in other ways, by descending modulatory mechanisms, etc. But at least one component of morphine tolerance is through this negative feedback loop. Of course these two loops can interact so that hyperalgesia can develop with chronic opioid administration. Sudden withdrawal of chronic opioid can in many cases cause hyperalgesia. Similarly, a chronic sensitized state such as that produced by neuropathic pain may develop resistance to morphine. Whereas someone who has neuropathic pain may continue to respond. This phenomenon has been tested in rat models. described. Rats with chronic constrictive injury of the sciatic nerve have a sixfold displacement to the right in their dose response curve to morphine – so they are already resistant to morphine prior to the first dose of morphine. This can be prevented by co-administering an NMDA receptor antagonist with morphine, i.e., MK801 plus morphine given intrathecally can prevent this shift of the dose response curve of CCI rats. Other experiments show a commonality of cellular mechanisms. I showed earlier that in some cases of neuropathic pain there seems to be a breakdown of inhibitory mechanisms. One of the ways that this can occur is intracellularly – inhibitory synapses on the cell can be desensitized by similar kinds of mechanisms. Of course this is variable from one patient to another, because in some, one sees what looks like a breakdown in inhibitory mechanisms, but not in others. There is great heterogeneity in these mechanisms, expressed in part by the diversity of what goes on intracellularly in each pain state.

11. Autonomic changes in stroke and CRPS

F. Birklein

Erlangen, Germany

Patients with stroke, besides having obvious motor and sensory impairment, also have changes of autonomic function in the paretic limb. Previous studies at our hospital have revealed that about 70% of stroke patients suffer from an acute edema on the paretic side, and about 40–50% of those also show hyperhidrosis on the paretic limb. This is a picture of autonomic changes

which resemble those one finds in CRPS patients. The aim of our study was to compare these two groups by measuring their symptoms.

We studied 17 stroke patients who suffered from acute brainstem or cerebral ischemia (hemorrhage was excluded). All had signs of autonomic dysfunction – edema, hyperhidrosis or change in skin temperature – but none had peripheral neuropathy or any preceding trauma in the affected extremity. Mean age of the group was 64 years, lesions were 8 on left, 7 on right, and 2 were in brainstem. This group was compared with 21 CRPS I patients, using criteria developed by Stanton-Hicks et al. The mean age was 55; initiating events in all patients were 14, fracture; 6, surgical trauma; and 1, soft tissue injury. Time after onset in all CRPS patients was long – about 75 weeks, so we are concerned with a chronic group. Twenty-one healthy subjects were used as a control group.

The clinical findings are as follows; there were no signs of spontaneous or evoked pain or allodynia in the paretic limb of stroke patients. Other findings between the groups were quite similar. Twelve of 21 patients demonstrated motor impairment in the painful limb and deep tendon reflexes were also enhanced.

The next figure shows the results of sweat measurements. Dry nitrogen gas was introduced into chambers covering 5 sq cm of skin. Changes in relative humidity in the efferent stream were measured. Sweating could be stimulated centrally by the intake of 0.5 L of hotfruit, tea, or heat radiation to the face and upper trunk of the patients. This is a thermoregulatory sweat test. Iontopheresis of carbachol was also used via a separated canal in the middle of the sweat chamber. This elicits a purely peripheral sweat response.

In this figure, a typical response in stroke patients can be seen. In the paretic limb, sweating was enhanced compared with the healthy limb. Quantitative sudomotor axon reflex test (QSART) after a latency of 2–3 minutes elicited a rise in the relative humidity leading to symmetrical responses in this patient. Of course we did expect this because we excluded any peripheral neuropathic changes in these patients. The response to carbachol is sustained, because it is not destroyed by the acetylcholine in the periphery.

Skin temperature in stroke patients was monitored with thermography. Simultaneous images of the ipsilateral and contralateral sides were recorded 15–20 minutes after the application of carbachol. We calculated mean temperature in an area of about 4 sq cm on the dorsal aspects of both the healthy and the affected limb.

In stroke patients we see reduced skin temperature that reached statistical significance, and enhanced sweating on the paretic limb – also of statistical significance. Identical patterns were found in CRPS I patients. Controls showed no side to side differences.

Summarize:

Stroke and CRPS I patients show a similar pattern of autonomic dysfunction. From the literature the assumed mechanism in stroke patients is a central sympathetic disinhibition of the sudomotor and vasomotor systems. From these studies we found at least indirect evidence that autonomic changes in CRPS can be explained also by CNS dysfunction. The assumption that adrenergic supersensitivity or inflammatory processes in the periphery may not be necessary. We believe that the autonomic disturbance can be located in the neuraxis – the brainstem or higher.

12. Sympathetic blocks and arousal stimuli in patients with CRPS

P. Drummond

Perth, Australia

This study aimed to investigate the changes in pain intensity in response to transient increases in sympathetic nervous activity. It should be possible to predict response to sympathetic blockade by the response to sympathetic arousal, or activating stimuli. The premise is that if pain is increased when sympathetic activity increased, sympathetic block should block pain.

Initially, it was necessary to establish the point when pain actually increased as a result of sympathetic arousal. Stimuli used were brief startle stimuli, a loud tone through headphones. Also used was application of a cold pack to the forehead for 20–30 seconds. Both types of stimuli were tested in 38 people who developed CRPS after various injuries – 18 had a damaged joint, sprain or fracture of a limb; 11 had had a sharp blow or crush, such as falling heavily, eg on the foot or ankle. In two others symptoms started after burn injury, and in 7, after a laceration or injection. Type I or II – in some it's difficult to show definitely that major nerve injury was involved.. But the type of injury would suggest it might have happened. In 13 of 38 the condition was aggravated by surgery – this seems to be a common cause. Typical group with pain in arm or leg, associated with various signs of autonomic disturbance.

The figure shows the results of startle – tone, through headphones. Verbal pain ratings every 5 seconds both before and after startle. The value immediately before the startle was fairly representative of the background of pain – it remained fairly constant over the short period of two to three minutes that I asked them to give pain ratings up until the startle. Immediately after this, pain increased in the majority of people, but the figure shows that pain does increase immediately after a short, sympathetically activating stimulus. It stays up for some time – 20–30 seconds before returning toward baseline.

Following the application of cold to forehead – again a nice increase in pain ratings as the forehead became cooler and cooler. Pain ratings reflect the pain in the symptomatic limb as distinct from the pain that sometimes develops in the forehead when you apply cold locally. For 25 seconds of cold there's a drift upwards in pain again consistent with the idea that pain increase during sympathetically activating stimuli in this group of people. When the cold is removed the pain ratings gradually returned back to baseline.

The next figure shows summary data. After the startle stimulus, pain increased in 21 subjects within 5–10 seconds of stimulus; no change in pain in another 14; pain decreased in none. In symptomatic limb there was a decrease in pulse amplitude corresponding to a substantial vasoconstriction, 52% on symptomatic side compared with same degree of constriction in contralateral limb. For those with no change in pain there was a similar degree of vasoconstriction. No significant differences were noted between responses on symptomatic and contralateral sides, either in the group with pain increase or in the other group with no change in pain. So a fairly consistent decrease of about 50% in pulse amplitude in response to the startle stimulus, indicating that it was a good sympathetically arousing event.

Cold. Pain increased in 14 of 35; no change in 19; decreased in 2. Some dissociation can be noted here, a small group where pain decreased when cold was applied. Perhaps this is because of some form of counterirritation as cold is applied, but we can see a minor degree of vasoconstriction in these. Nevertheless, we have constrictions that are highly statistically significant, about 20% in the group as a whole. No difference again between symptomatic and contralateral sides, either in the group whose pain increased or in those with no change or a decrease in pain. Again, it demonstrates that applying cold to the forehead increases the vasoconstrictor output to the limbs.

The following results are quite different from those without this chronic pain condition. In this model, capcaicin was applied to the forearm and then radiant heat was applied to the treated skin. The thought here was that perhaps there might be a peripheral interaction between the sensory and sympathetic nervous systems which would serve to increase heat hyperalgesia. This idea was based on some other experiments, in which noradrenalin is infused into capcaicin-treated skin it increases thermal hyperalgesia. In fact when you use a substance which releases endogenous stores of noradrenalin – such as tyramine – there is also an increase in heat hyperalgesia but no increase in spontaneous pain. If I use startle, or cold is applied to the forehead this should lead to a peripheral release of noradrenalin in the capsazin treated skin which would increase heat hyperalgesia but I was sadly disillusioned because there's a clearly dramatic decrease in pain ratings in these people while cold is applied to the forehead – a decrease of 5–6. We established how hot the heat lamp had to be to get to this level of rating on a 10-pt numerical rating scale, before we started the cold stimulation. After the cold was taken off there was a gradual return with pain ratings toward baseline and this took on average about 25 seconds. There are several possibilities for this decrease in heat hyperalgesia when cold is applied to the forehead: when they had to think about cold up here it took their minds off heat on the arm – a distraction; that doesn't explain why it took so long for pain ratings to return toward baseline though. I suspect there is another effect. The point is that the decrease in pain ratings contrasts very markedly with people having CRPS, where pain ratings increased when cold was applied to the forehead. This figure shows much the same result for startle stimulus. Again the experiment was the same. Applied heat to capcaicin-treated skin with cold forehead was followed by a decrease rather than increase when they were startled. This contrasted nicely with the effect in CRPS.

Does sympathetic blockade influence the increase in pain ratings in response to startle and cold? Summary of 11 patients is shown in this figure. Ratings of background pain did not change significantly after sympathetic block – 3.7 to 3.0 – on average. Tests were done within 2–3 hours of sympathetic blockade. Usually on morning before block, then after lunch.. Increase in pain to the startle stimulus did subside after sympathetic blockade, so there was a significant decrease in the group, on average, after a lumbar or stellate ganglion block. This is consistent with the idea that perhaps sympathetic blocks do inhibit any increase

in sympathetic outflow that otherwise would somehow induce pain in the symptomatic limb. There were suggestive trends – no change here in cold pain perhaps because cold pain did not increase very much in this group of 11. Suggestive trends that were not significant statistically – for cold allodynia, induced by applying a copper bar, cooled to about 2 C, to the affected limb. Also a suggestive trend in decreases in those reporting brush allodynia – 6 of 11 before the block, vs 2 of 11 after the block. No change in Von Frey thresholds, to pressure pain applied with an algometer, or in heat pain thresholds, measured using radiant heat lamp in sympathetically blocked and non-blocked limbs. There is a significant decrease in startle pain from before to after sympathetic block.

The next figure shows the pain rating before and after startle in 11 patients after sympathetic block. In one patient before sympathetic block there was a substantial increase in pain rating to loud tone – from 5 to 10. After block, background pain was rated as 7. In other patients pain went up in response to loud tone – but was eliminated by sympathetic block.

In some patients, a very good response to sympathetic block with temperature increases of 11 degrees had no effect on startle response. So in these patients there was little correlation between what the sympathetic nervous system did in response to sympathetic blockade and the patients' pain ratings in response to a startling stimulus.

Another observation was the fact that there was no indication of sympathetic blockade having any effect on the normal vasoconstriction that develops in response to a deep breath – despite fairly good signs of sympathetic activity on other modalities.

This person has vasomotor signs of sympathetic blockade on the right but still shows substantial vasoconstrictor responses so that it is possible to achieve what appears to be a partial sympathetic blockade between different modalities.

Conclusions. Heat pain usually decreased in healthy people when startled or cooled, but background pain often increases in CRPS patients when startled or cooled, so there's a dissociation between controls and CRPS. But because this effect didn't seem to be related to the effectiveness of sympathetic blockade the increase in pain seems to be mediated at least in part by some other mechanism bedside sympathetic discharge.

13. Hemisensory impairment in patients with CRPS

O. Rommel

Bochum, Germany

Type I CRPS is characterized by regional pain and sensory changes in response to a predominantly traumatic, noxious event and is associated with abnormal skin color, temp changes, abnormal sudomotor activity and edema. Sensory changes are reported to occur in about 70% of patients with CRPS. However, studies conducted so far have concentrated on the quality of sensory impairment and there is only limited information on the extent of sensory impairment and possible proximal spreading. The clinical findings in two patients with hemisensory deficit in CRPS prompted us to perform a clinical study in 24 patients with CRPS I, which was published in PAIN in Spring of this year. In this study we found a hemisensory impairment ipsilateral to the affected limb in eight patients, with a decreased pinprick and temperature sensation on the whole body side, including the face. In four patients we found sensory deficit in upper quadrant, and in eight this was limited to the affected limb. Mechanical allodynia and hyperalgesia were seen, as well as the motor impairment to be more frequent in patients with generalized than in those with localized sensory impairment, and the generalized sensory impairment was more frequently documented in left sided than in right-sided CRPS.

To confirm clinical findings and correlate them with neurophysiological findings and psychopathology, we conducted a second study in 40 patients with CRPS I. The majority of patients had their illness for more than 12 months in 27 and less than 12 in 13.

In all, history was taken and neurological exam performed. Neurophyscological recordings were performed in all patients, but not all tolerated every measurement. Nerve conduction velocities were obtained in 37; sensory evoked potentials after tibiae or median nerve stimulation in 33; sympathetic skin response in 38. To perform quantitative sensory testing (QST) we applied (Von Frey hairs) in all patients in different locations on both sides; in 28 we performed quantitative temperature testing with a thermode. The Peltier thermode was applied to five different locations on each body side, and the temp of this metal plate was increased from 32 to up to warm threshold reached and then decreased until cold threshold. This was repeated five times on each location and afterwards the threshold for heat-induced pain was determined. In 36 patients extended psychiatric exam was performed using SCID–a structured interview for DSM-III R. Interviews were performed by a trained psychologist – 60 to 90 minutes

each. And they concentrated on affective disorders, psychosis, OCD, neurosis, etc.

The study was just finished a few days ago, so I will present preliminary findings. With respect to sensory impairment, we found a hemisensory impairment in 12 patients; in 3, a sensory deficit in upper quadrant; and in 25, a sensory impairment limited to the affected limb.

Similar to our first study, we found that a high percentage of patients with generalized sensory impairment had mechanical allodynia and mechanical hyperalgesia. However, with respect to the body site of sensory impairment, we could not confirm our results from the first study because in this study we found sensory impairment in left and right sided CRPS. With respect to illness duration a generalized sensory imparirment could be found in patients with very longstanding chronic as well as in those with duration of less than 12 months.

Quantitative testing results are as follows. In 8 patients with clinical finding of hemisensory impairment ISPs to affected limb we found increased threshold for warm and cold temp on the ipsilateral body side. E.g., CRPS on left: an increased threshold most pronounced on left – and threshold for heat induced pain was increased on each location compared with the other (non-affected) side. In four patients there were no distinct differences between sides, but one patient had hemisensory impairment limited to the affected limb in a glovelike distribution but had a difficult disease course, with relapse, swelling, etc, and reported radiating pain going to his face and eye – no finding of hemisensory impairment but the threshold for warm and cold temperatures was increased on the ipsilateral side.

The next slide shows neurophysiological recordings – pathological or abnormal findings in about one third of all patients for each method used. No differences between generalized and localized were observed.

Psychiatric findings: most important finding was an increased frequency of patients who fulfilled the criteria for major or minor depression – 18 in all. No psychiatric characteristics for any patients before the onset of CRPS were found. In one third of patients, stress factors could be identified at the beginning of CRPS.

To illustrate our findings, following is a case report. In April 1998, a 40-year old woman sustained minor trauma to the right hand, and developed a full picture of CRPS I with swelling etc. As symptoms persisted she was sent to our Pain clinic, where she received oral medications, physical therapy and sympathetic blockade. When I first saw her in January of this year symptoms had improved somewhat, with intermittent pain, swelling and difficulties in stretching her fingers. She had, however, developed hyperalgesia and hyperesthesia in a glovelike distribution in her right hand. She wanted to go back to work and I lost contact with her. All the neurophysiological exams were normal. A few weeks ago a colleague contacted us and said he had seen a patient with hemisensory deficits – it was the same patient. She apparently went back to work but as a result of her occupation all her symptoms increased. In April she had a minor trauma to her leg – hit it on a table – in the following days she developed swelling and pain, but it was different from the pain in her right hand. The pain in her right hand increased even more, with burning, and it got worse and worse. She had pain on her right back, and she said she had the feeling of being divided in two halves, with a numb feeling on the right side of her body. With testing there was an increased temperature threshold for warm and cold. Neurophysiological recordings were normal.

Conclusions: The generalized sensory impairment as well as the mechanical allodynia and hyperalgesia observed in our patients might indicate that central mechanisms are involved in the pathogenesis of CRPS. With respect to the fact that there is an ongoing discussion on central plasticity perhaps this may be a clinical finding that gives us a marker for this kind of central plasticity. With respect to hemisensory impairment this may be due to functional disturbances in noxious event processing in the thalamus – the thalamus because thalamic lesions are followed by hemisensory impairment.

Generalized sensory impairment observed relies on functional alterations – we don't have structural changes in central processing of noxious events and therefore the neurophysiological recordings reveal normal results in the majority of patients. Also, a high number of CRPS I patients developed minor or major depression in the course of the disease. However, no differences were found between patients with a generalized or a localized sensory impairment. Thus, the generalized sensory impairment is independent and cannot be explained by psychopathology.

14. Motor disturbance in reflex sympathetic dystrophy

G. Deuschl

Kiel, Germany

There are some new data. I will summarize what is

known about the motor disturbance of reflex sympathetic dystrophy (RSD).

Movement disorders of RSD consist of several aspects. Reduced grip power is found in more than 90 percent of patients. Some of them, less than 20 percent, have an increased tone; between 50 and 90 percent have postural tremor. Some of them, less than 20 percent, have spasms. Some have dystonia, and a small minority have a clinical syndrome which is treated in parallel by pain and movement disorder specialists – the dystonia syndrome.

Tremor: A study in the late 80s compared tremor in patients with CRPS I and normal subjects. We found that on the affected side there was usually a profound tremor which is about 1 or 2 orders of magnitude higher than on the unaffected side. It usually comes with a tremor peak also in the EMG which tells us something about the generating mechanisms.

About 20 patients were included in the study. Tremor is found in the majority of these patients. On the unaffected side, there was no tremor; large tremor amplitudes were found on the affected side. During the symptomatic stage of the disease the tremor is variable, and after recovery from RSD there is normalization of this kind of movement disorder. The frequency found in this tremor is exactly the same as that found in enhanced physiologic tremor, which has very different causes.

The next figure shows generators of tremor. On the unaffected side there is clearly a reduced frequency. On the affected side, there is a similar decrease in frequency but there is a peak in the EMG between 8 and 12 Hertz, the frequency of enhanced physiological tremor. And you can see this peak again in the axillary rotators, telling us that there are two components of this tremor – the mechanical one which is decreasing its frequency, and a neural one, which is due to this EMG peak. We know much more about this EMG peak, that it is basically a phenomenon coming from cortical sites. We then looked at the effect of sympatholytic intervention – after a stellate ganglion blockade this tremor is completely abolished. Putting these findings together we can summarize that this tremor has the frequency and activation characteristics of a physiologic tremor. So we could call it an enhanced physiologic tremor. Furthermore, we have evidence that the sympathetic nervous system is interfering in some way and is probably a factor in causing this kind of tremor. One possibility that we also know from a very different condition – hyperthyroidosis – we know there is an intense sympathetic innervation of the muscle spindle, and it is possible by this mechanism that tremor is produced. We are aware that the sympathetic nervous system can increase the sensitivity of the muscle spindle, thereby creating a loop which generates this. However, the findings I've shown, with the increasing peak of the EMG, indicate that there are many other mechanisms, among which is probably a cortical one. During the last five years a number of papers concerning the movement disorders in CRPS have been published. Some of these express the conclusion that a possible kind of a neglect syndrome could be present in CRPS I. I have some problems with this interpretation. To summarize what we understand about neglect – the unilateral neglect syndrome is a selective disorder of awareness that gives rise to strikingly disordered behavior. Loss of awareness of the neglected side, i.e., unawareness of information from the neglected side is not used. Neither input from this side, nor orientation to this side, nor action to this side is performed. The neurospsychologists separate between motor and sensory neglect, but even if this is accepted there is one critical point; the primary sensory areas and primary motor areas of the cortex may not be involved when we talk about neglect. So I seriously question the interpretation of what we find in RSD as being the result of neglect. Hypothesis: dealing much more with sensory motor integration within these primary sensory areas. What we did is investigate a simple lifting movement of the hand.

What we are now using is an apparatus that was constructed ten years ago – a simple device which assesses the position grip – we are measuring the force of the fingers and the force in a vertical direction. There is a good resolution of these forces which basically assesses the capacity of a human to grasp a blueberry. The question is, does the patient with RSD have blue hands after grasping blueberries?

In these patients we found that grip force increased. The symptomatic side and asymptomatic side were both abnormal in this paradigm. What is wrong in this precision grip in RSD? The preload duration – from when finger touches to the beginning of lift. Contact with the object is somewhat disturbed in this condition. Whereas the load duration – the simple lifting – seems to be normal.

The next figure shows grip force at peak. This is clearly enhanced, and even at the start of load there is obviously something wrong with it. So, these patients start having difficulties to get a tight grip. They begin with a higher grip force before actually lifting the object. This demonstrates that the grip force and load force quotient and ratio of these parameters is abnormal both at peak and already in the early static phase.

The third abnormality is that there's something going on in the static phase. When the object is lifted and the patient keeps the object about 10 cm above the table. At this time we have a variation of the grip force which is much higher than in the normal subject, and this is due to tremor, which is developing in this condition and correlates with what we found in the earlier study – a clearcut postural and a movement-related tremor.

So far, these preliminary data show that there is something going on with the sensory motor integration of this type of movement. One can only look at another condition where there are similar abnormalities and that is dystonia. If we took patients with writer's cramp, we would find the same abnormalities. The movement disorder is different. They have problems with writing and they have it selectively during these fine manipulations, but the quality of the movement disorder is the same. And we know a little bit more about this movement disorder from an animal model of writer's cramp. This is a monkey model in which the monkey is asked to move a handle, and this handle is continuously stimulated so they have a continuous afferent input, like in RSD where there is a continuous pain input and maybe many other different afferent fiber inputs. What the monkey does after having been exposed to this paradigm for several days is to not get better, but rather deteriorate. The underlying cause for this is not a neglect – it's a change of representation in the sensory and motor cortex.

In this next figure, a strain in the fourth figure is represented over a much larger area of the sensory cortex. The idea is that once there is a continuous afferent inflow into the sensory motor cortex there is a plastic change going on there which in turn causes a secondary process – a movement disorder.

The differences and similarities between CRPS I and dystonia are as follows: The power is clearly reduced in CRPS I but is rarely reduced in dystonia. Sensory disturbances are present in CRPS I and we have very similar disturbances in dystonia. Pain is mostly present in CRPS I, but rarely in dystonia – additional symptoms such as tremor, spasms, rigidity, enhanced tone – are present in both conditions. The full-blown expression is a fixed dystonia, not painful, and it's the causalgia dystonia syndrome in CRPS I. I'm aware that this is only a hypothesis, but it is the only one that can be tested because there are means like the kind of test I showed you to assess the functional properties on the finger grip, and there are means like functional MRI where we could label the area that is covered when one gives defined stimuli. Therefore, I believe that it's worthwhile to look at specific abnormalities in CRPS– probably we will learn much more about the functioning of different movement disorders by concentrating on the foregoing aspects.

15. Disorders of sympathetic functions in CRPS

G. Wasner

Kiel, Germany

We are looking at vasomotor disturbances in CRPS.

Slide: Vasomotor disturbances seemed to be caused by dysfunction of the sympathetic nervous system and they may play a crucial role in the symptoms of sympathetically maintained pain.

Definition – I after trauma, no lesions, formerly called RSD, Type 2 develops after definable nerve lesion present.

Focus on autonomic system – abnormalities in skin temperature, bluish and sometimes reddish hand that's sometimes warm or cold. Sweating and edema. Skin temperature differences.

Underlying pathophysiological mechanism that was thought to play an important role in these vascular disturbances. Physiological regulation – sympathetic pathways, preganglionic neurons projecting into postganglionic neurons and innervating the vascular bed of the skin.

It was thought that the underlying pathophysiological mechanism is something like an overactivity. We learned today that sympathetic vasoconstrictor neurons develop spontaneous activity, especially in the vascular bed of skin, and reflect thermoregulatory stages. And it was thought that there could be an overactivity in sympathetic pathways, leading to a vasoconstriction in the vascular bed of the skin, with development of autonomic and dystrophic signs, blue, cold hands, etc, and that a coupling to nociceptive afferent nerve fibers might be a source of sympathetically maintained pain in the periphery. Some clinical observations don't fit perfectly with this hypothesis of overactivity. For example, it is often described that in the early stages of CRPS we don't have cold hands, but warm hands – this doesn't fit with hypothesis of increased sympathetic activity leading to vasoconstriction. And the other thing is that it is very difficult to correlate these vascular abnormalities with symptoms of SMP in patients. So this is reason to investigate the autonomic and vascular disturbances in the patients.

Slide: We did this in 3 groups. The first were 20 patients with CRPSI – we had ten patients with chronic painful limbs and other regions were seen by Orthopedics, Anesthesia, etc. There were ten healthy controls. Sympathetic function – how to look at skin sympathetic function? We went back to the physiology of nerve fibers. The sympathetic vasoconstrictor fibers innervating the vascular bed of the skin are involved in thermoregulation. This means in a cold environmental temp these nerve fibers are activated, producing a vasoconstriction due to release of noradrenalin. The biological aim of this is not to lose temperature in cold conditions. The opposite happens on a hot day, then the sympathetic vasoconstrictor activity is inhibited. Noradrenalin decreases and we come to vasodilatation with a biological aim not to overheat. We can imitate these conditions with a thermal suit, which has tube that can be perfused with either cold water or warm water. We can switch on vasoconstrictor activity in a controlled manner. When we perform these measurements in normal subjects we see the following online recordings.

With whole body cooling, sympathetic activity increased causing decreased skin blood flow due to vasoconstriction. Alternatively, from high sympathetic vasoconstrictor activity during this cooling stage, a large increase in skin temperature can be induced by inhibiting sympathetic vasoconstrictor activity and increasing the blood flow. In healthy controls there are no real side differences, meaning that the regulation is mostly symmetrical.

The next figure shows the results of a patient with CRPS. The same measurements were performed. Cooling, warm up etc. During cooling there's a decrease in skin temperature which was expected due to vasconstrictor activity and after this the temperature increases again because this activity is inhibited. When we look at the side with CRPS it was an upper extremity, we measured the temperature at the fingertips and we see at the beginning the temperature was higher, about 2 degrees. The decrease in temperature was not as fast as in the contralateral side, but when we stopped the sympathetic vasoconstrictor activity the increase was much faster. During these controlled alterations of sympathetic activity large side differences in skin temperature develop, eg, contralateral temperature about 25 degrees, similar site in disturbed limb is 32 degrees. This is not a stable static difference. Skin temperature differences seem to be dynamic, and at the end of full body warming, when there's no sympathetic vasoconstrictor activity anymore there are very few side differences.

We observed cold patients, too. Here we started with whole body cooling and on the contralateral side we see a good decrease in skin temperature due to vasoconstriction and after inhibition of sympathetic activity the skin temperature increases again. The disturbed limb – already cooler at the beginning. After whole body cooling we performed whole body warming and the increase was not as fast as at the healthy side. Also, we see huge side differences; eg, here 26 degrees on the disturbed limb and 32 on healthy one. Again we see dynamic component – when we look here there are only a few temperature differences. During the entire maneuvers the temperature of the disturbed limb was cooler and we named this patient the cold patient.

Third type of regulation – the intermediate patients. They are characterized by a crossing of these two lines – though in these patients the disturbed side was warmer at the beginning but then the decrease of temperature was much faster than at the contralateral side and then increased much faster again. So we identified three different groups although they all underwent the same manoevers. During these controlled alterations we see large side differences that have similar dynamic components and a few side differences when the sympathetic nerve activity is totally abolished. To address these phenomena we analyzed the absolute differences of skin temperature independently whether the temperature of the disturbed limb was warmer or cooler.

Slide: Skin temp of healthy extremity as a reference. 25 degrees on healthy side means increased vasoconstrictor activity because of whole body cooling, and here there's no sympathetic vasoconstrictor activity (at 35 degrees) at the end of whole body warming. What we can see here are the differences in side temperatures between the healthy side and the affected side. The absolute value is independent of whether it's warmer or cooler, so at this stage we have an average difference of about two degrees in this patient. When we took this point here, which is about mid-range of the underlying sympathetic activity, we got large side differences of about 3 degrees. But the more the sympathetic vasoconstrictor activity is inhibited the less side differences we got. So this may be the reason why many observe that the side differences are not as reliable as markers for this disease. It might be possible that at one day you'll see the patient at one stage and the next day, warm day, there won't be any side differences present because of this dynamic component.

Green line – healthy controls. We can't see any huge side differences and no dynamic component below one degree during controlled regulation of sympathetic activity. And the same accounts for the controls with the disturbed limb – non-CRPS. So similar results in blood flow.

Slide. Blood flow measurement. These are relative units. . . value of 1 means difference in blood flow of about 100%, 0.5 means 50%, etc. We see similar characteristics – a dynamic component in patients with CRPS but not huge side differences in healthy controls or in patients with pain of other conditions. You might argue that there are some fluctuations – we are not sure why, maybe underlying pain. For this reason we think the dynamic component seems to be very specific for patients with CRPS.

Warm, cool, intermediate. Group results. We calculated duration of disease in months when we investigated those patients and found significant differences. The mean duration of the warm patients was about 3 months, whereas intermediate patients was 8 months, and the cold patients was 31 months. Acute CRPS patients are warm patients. If we look at each patient separately, eg this one increased by a maximum of 6 degrees, etc. there is a significant relationship between duration of disease and dependence of the warm and cool state.

This next slide shows an early patient. Skin blood flow and temperature on the healthy side. Clear vasoconstriction and decrease in skin temperature. On the disturbed side, no alterations at all. 50 minutes of whole body cooling evoked no change in the disturbed limb.

Skin temperature in whole maneuver – whole body cooling, resulted in a clear decrease in skin temperature on the healthy side; whole body warming – no differences were seen in limb with CRPS. A similar result was seen with a short-term activation of sympathetic vasoconstrictor activity. Deep inspiratory breathing leads to activation of sympathetic vasconstrictor neurons – here every inspiration was associated with vasoconstriction in the healthy limb. In the affected limb there was no vasoconstriction at all. We feel this reflects total inhibition of sympathetic activity in this patient. Three weeks later, sympathetic vasoconstrictor activity returned in this patient.

Our results provide sympathetic evidence that in acute CRPS spontaneous activity is diminished. This is the reason why we see vasodilatation and warm hands. Our results are in agreement with Drummond (1991) who reported decreased levels of noradrenalin and neuropeptide in the disturbed limb, both markers of sympathetic activity. Curvis et al. in 1995 found decreased short term sympathetic vasoconstriction in acute CRPS. Recently, Schurmann et al. have shown that in acute CRPS there seemed to be diminished sympathetic vasoconstrictor activity. What about chronic CRPS – is there any place for overactivity in sympathetic vasoconstrictor neurons?

We conclude that this is the underlying pathophysiological mechanism in chronic CRPS. We have discussed inhibition of sympathetic activity during the acute stage, and maybe this is the reason why during this stage there's development of supersensitivity, and when sympathetic activity returns there will be more vasoconstriction. Maybe there's also the chance that, when sympathetic activity is inhibited, alpha adrenoreceptors develop on the nociceptive afferents. So this could explain SMP. There are two problems with this model. First, animal experiments that have demonstrated the development of supersensitivity in a condition where there's no sympathetic nerve activity but the whole system is intact – is missing. And second there is no explanation for patients who seem to respond to sympathetic blocks for SMP.

Summary: Vasomotor disturbances in CRPS: evidence for central inhibition of sympathetic vasoconstrictor neurons in acute CRPS, but possible that secondary changes in the periphery lead to vascular changes in chronic CRPS. The dynamic vascular abnormalities depend on sympathetic outflow and seem to be specific for CRPS.

16. Supermotor systems and afferent nociceptive function in CRPS

F. Birklein

Erlangen, Germany

Slide: CRPS develops after noxious events. These events – trauma, surgery, stroke – CRPS is typically described as a triad of autonomic disturbances, pain, hyperalgesia – sensory disturbances; and motor disturbances.

Slide: We saw 200 patients and analyzed 145 clinically. Most were seen in acute stage of disease. We found abnormalities of the sympathetic nervous system in about 98%; edema and differences in skin temperature, color, depending on the stage of presentation. Sweating abnormalities occurred in 55%.

Slide: Woman with sweating at room temperature after fracture of ankle.

Slide: Acute case of CRPS after cast showing discoloration etc.

Slide: How we measure sweating. Sweat chambers covering 5 sq cm of hairy skin, fixed to ipsilateral and contralateral sides of the body, and the nitrogen gas is passed through the chamber with a constant flow.

Slide: We measured skin temperature at the same time in our study. We have restudied several subgroups.

Slide: This shows increased sweating after both central and peripheral stimulation by sudomotor axon reflex test (QSART). These cases were very acute with duration of CRPS mean of 7 weeks.

Slide: Measurement of skin temperature in this subgroup revealed that after very controlled thermoregulatory conditions – the patients had two hours time for aclimatization – reveals an increased skin temp in all but two of our patients, and we know from the literature that an increase in skin temperature interferes with sweat protection also in peripheral sweat tests. That's why we restudied our patients 18 months later. Then, the skin temp was found to be significantly decreased in the same patients. Pattern of sweating during the acute stage is increased in TST; increased sweating after peripheral stimulation; at follow-up, sweating was less pronounced in acute stage but was induced by thermoregulatory stimulation; no side differences were found in quantitative analysis.

To summarize: In very acute patients, we found an inhibition of vasoconstriction indicated by an increased skin temperature. And we found an increased sweat output indicated by an increase of sudomotor function – this means the sympathetic nervous system is differentially altered – it's not simply overactive or less active. This is the first idea we had – that this pattern of autonomic function must depend on a disturbance of thermoregulatory function in the CNS, otherwise it can not be explained.

Slide: Another attempt to show impairment of vasoconstriction. Different tests of sympathetic reflex vasoconstriction were used. First attempt we used venoarteriolar reflex, acting as a purely peripheral axon reflex since it works on the nerve plexus. We used phasic vasoconstrictor – inspiratory gasp, causing a phasic vasoconstriction presumably by spinal or medullary pathways. We tested the patients with the cold pressor test, the test depending on cold pain afferents, spinal reflexes and hypothalamic reflexes and we asked our patients to perform mental arithmetic. Mental arithmetic is a weaker stimulus for vasoconstriction and is purely cortically generated.

Slide: This shows quantitative analysis. We found no differences when only peripheral reflexes are tested and no differences when the spinal pathway is involved, but we found significant impairment of sympathetically mediated vasoconstriction when a weak cortical stimulus is applied, as compared to the contralateral side. Patients were compared to age and sex matched group of healthy controls. The implication is that vasoconstrictor activity is inhibited and sudomotor function is enhanced and I believe these data clearly show that the crucial point for this pathophysiology must be the CNS.

Slide: We looked at these phenomena another way. Stroke patient is a human model of autonomic disturbances of pure central origin. We found an increased sweating after thermoregulatory stimulation, we found no difference in sweating with peripheral stimulation and we found a decreased skin temperature – exactly the same paradigm as we found in CRPS patients in the chronic stage, and slightly different from CRPS patients in the acute stage.

To summarize so far: First, we found a central disturbance of the autonomic nervous system in CRPS. We also found that secondary peripheral mechanisms must take place in this disorder to explain first, the exaggeration of sudomotor function during the acute stage, reflected by the increased level of sweating due to peripheral stimulation. But we don't need a peripheral supersensitivity hypothesis to explain the decrease from the temperature rise early in the disease to the decreased temperature in chronic CRPS , because these phenomena occur in pure central pathophysiology too.

Slide: This is the first conclusion. In acute CRPS there is an increased sudomotor and a decreased vasomotor activity. We believe the primary reason lies in the CNS. As far as the sudomotor system is concerned, we propose that secondary peripheral mechanisms have to take place to explain the full clinical picture of CRPS and possibly cannot exclude that peripheral adrenergic innervation supersensitivity might develop in the course of the disease. I believe that this is a secondary phenomenon. The question is, how does sympathetic dysfunction lead to pain and hyperalgesia in CRPS?

Slide: To address this question we devised the following experiment. Shows impact simulator, designed by Institute of Physiology. It allows us to deliver brief impact stimuli to skin. Could be in noxious range, single shots or trains of shots can be delivered. A pinching device to pinch finger with a force of 8 newtons.

Slide: Results in 40 patients with acute CRPS. We found no systematically altered heat pain thresholds in these patients. We found no altered responsiveness to pinching; we found a marked decrease of threshold for impact stimulation on the affected side.

Slide: Accordingly, when we delivered five trains close to the threshold range on both sides with an interstimulus interval of about 5.5 seconds we found a significant windup on the affected side not seen on the other side.

Slide: We restudied 8 patients before and after the application of aspirin and found no alteration of pain thresholds to impact stimulation. This led us again to assume that in CRPS there is strong indication for a central sensitization to nociceptive function and we found no direct evidence for inflammation in this disease.

Slide: How could this central sensitization be driven? We have to look to the periphery. This is a point where our Dutch colleagues helped us. There are several lines of evidence that oxygen supply may be impaired in CRPS. This may be due to perfusion deficits due to the sympathetic failure. This has been suggested previously. The nutritive blood flow is impaired in these patients. We also know that low pH – from inflammatory mediators is involved in the generation of pain and the activation of nociceptors, and free oxygen radicals could also be involved in the generation of mechanical hyperalgesia. We developed a simple model – constant infusion of low pH synthetic interstitial fluid, pH range 6.1, and infused it intradermally. You can see localized edema, and we infused it also intramuscularly into the affected and unaffected sides.

Slide: Shows that the time when pain starts due to acidosis of tissue might be an artifact due to the elasticity of the infusion site and rigidity of the skin and the tissue. We analyzed 10 minutes of low pH pain. This is a typical response. A curve with highly increased pain on the affected side. Quantitative analysis of intradermal stimulation – is significantly increased pain due to low pH.

Slide: Shows increased pain due to intramuscular stimulation – increased at all times during stimulation period. From these 10 patients 8 complained about deep pain, not superficial, and all 8 said that this evoked pain reminded them of their ongoing CRPS pain. It was not our attempt to directly measure low pH in tissue, but raw data of low pH effects. We performed microdialysis in the skin of controls and patients. The lactic acid is increased in CRPS patients. This could be the endogenous source of brotones that could provide a possible indirect link between sympathetic nervous system abnormalities and pain and hyperalgesia on the other side. Our attempts should focus on this linkage in the course of CRPS, unless structural changes along the neuraxia – change the pathophysiology of this disease.

17. Introduction: diagnostic criteria

P. Wilson

Rochester, MN, USA

One aim of changing the classification a couple of years ago was to have better criteria for the diagnosis and we mainly based the definition on signs, symptoms and history, not on lab testing. Let's all look in the future. We have to reevaluate our testing and when I listen to the talks at this meeting – eg, three-phase bone testing, but we don't have data on this test in CRPS patients. Many more things – laser Doppler flowmetry thermography, etc.

Slide: This is a scan with labeled immunoglobulins, autography, what they showed was a leakage of the immunoglobulins in these tissues indicating that there's an inflammatory process underlying this disease in the acute phase.

Slide: The big controversy of SMP – how can we define SMP, predict SMP? Is there a predictor? Patients with causalgia in CRPS I and II grouped together in this slide. Initial pain relief due to sympatholytic interventions. If you group all these patients, papers, together you find initial pain relief of nearly 90% due to sympathetic interventions. This is good but there is much controversy on this issue. On the other hand, if you look at long-term pain relief in these patients it's much less in this group and we have to keep this in mind – what does it mean, a sympathetic component? The major aim we have in the future in terms of diagnostic criteria in the disease and of diagnosing the SMP component.

Retrospective study – Philip Low developed quantitative sudomotor axon reflex test (QSART). The first part of it was a retrospective review of some 400 patients gathered out of a series of about 1,000 upper extremity pain and dysfunction syndrome patients that we had enough data on, and that led to a prospective study of 100 plus, in an attempt to validate the diagnostic criteria, but I was also going to present another case report. Reading what Norman Harden has to say is more important. The work we did at the clinic, I'm reminded of the apocryphal story of the drunk crawling around late at night under a streetlight, the policeman says, what are you doing, he says I'm looking for my car keys. Where did you lose them? Over there, but there's more light here... Perhaps that's what we're doing at the Mayo Clinic! Another practical request that has been made from our constituency, clinicians in the trenches; please give us a system that we can use at the bedside and defend in court, and that we can do for almost no cost. Because of the list that Ralf Baron just put up, the traditional one – bone scan, iv testing,

x-rays, neurologic workup, motor testing – adds up to about $10,000 and the Workers' comp people are not paying for, but are expecting us to produce a diagnosis essentially for nothing. The Mayo Clinic data in the handout suggests that we need to be able to measure the sympathetic dysfunction in some way rather than take the patient's word for it – we need some objective measure that can be validated in light of what is found in the laboratories. My plea – listen to Norman Harden and help those of us who are in the trenches diagnose this condition cheaply and accurately so we can give the correct treatment.

18. Pathophysiological mechanisms of RSD

L. Van der Laan

Tilburg, The Netherlands

Slide: We heard a lot today and when we summarize the ideas of pathophysiology which are accepted today. First, psychological/social; inactivity; sympathetic system – hyperactive, hypoactive or a place for altered alpha adrenoreceptor function; causalgia or CRPS II; or exaggerated regional response (suggested by Sudek in 1942). Maybe there is a combination of these five theories.

There's very little written about the motor manifestations of RSD – most papers are concerned with pain sensations, not weakness or limited function of the affected extremity. Very surprising. Most theories are based on the ligation animal model, various models. Sometimes there is exploration of the normal undisturbed neurophysiology. Very seldom really basic work. On the other hand we heard today some lectures of recent work with patients.

Slide: In 1985, we started with the criteria of RSD because we saw lots of patients with these complaints. Prospective data base. We say there have to be at least four of five symptoms – diffuse pain, difference in skin color, edema, skin temperature change, and limited active range of motion. The signs and symptoms are present or increased after exercise. These signs are present close to the area of operation or trauma, and also distal to this site. Veldman was first to come out with our results in 1993, with 829 patients. When we look at the patients within two months of the onset of their disease, most showed similar signs of inflammation. In this group, within two months after onset, hyperhidrosis, a sympathetic sign, was only present in 57%. Other signs not 100% present either. So we started to study these patients and see if there is an inflammatory response.

For this reason, we cooperated with our nuclear laboratory and used possibility to give patients IV labeled immunoglobulin. Normally it stays in the blood vessels – only goes out when there's a leakage between the endothelial cells, then it goes out of the vessels into the soft tissue. This is a sign you can see during inflammation, for example. When we performed this test, we can see that after five minutes in a patient with RSD of about 3 months duration there is an increase in the labeling in the hand affected by RSD.

Slide: We performed this test in 23 RSD patients, 17 with RSD present within 5 months after onset of signs and symptoms, so acute RSD. And from these, 14 had a positive scan, and three had a negative one. So it can help in the diagnosis but it is not always present. But for us it supports the theory of an original inflammatory response. After 5 months more in the chronic phase, the scan is negative in five and only positive in one patient. We also performed flux studies – to see how is the oxygen saturation of the patients by comparing them – the affected extremity of acute RSD patients with the contralateral normal extremity. There was a significant difference between them, so the oxygen consumption is impaired. Two years ago our group found similar results. We tried to see if it's possible to use a noninvasive technique to get more information about the energy state of these RSD extremity patients. For this reason we used the phosphonuclear magnetic resonance spectroscopy, which gives information about the energy state of the skeletal muscles. You can see that this picture shows a normal unaffected extremity. We can see the inorganic phosphate, and phosphocreatine that is the energy supplier, which provides the energy, and the three peaks of ATP.

When you exercise the healthy hand of an RSD patient – you can see that the inorganic phosphate increases and the phosphocreatine is diminished, so it will be supplied in this way. When the healthy hand stops exercising after about 2 minutes it will be normal again – you can see the increase of the phosphocreatine peak and the inorganic phosphate is decreased, so this hand can move again. On the other hand, the affected extremity – you can see that the phosphocreatine, the energy supplier, is decreasing and inorganic phosphate is very high, so this hand cannot move much more. When the patient stops the exercise the inorganic phosphate remains high and the phosphocreatine stays low. So after exercise there is less possibility for the patient

to move, ie, he's not unable to move but the energy supply is decreased. We also performed the technique in chronic ARD patients (11) and here you can see that in these the severe chronic ARD patients the affected extremity has a significant alteration of the energy state compared with the normal. So we have a few points providing us with information that there is an alteration in RSD patients. First of all the clinical signs; second, an increased permeability, third, decreased oxygen consumption in RSP patients, and we are lucky to have human material to investigate. We like this very much because we want to see what's happening to the nerve of the ARD patients and what's happening to the skeletal muscles of these patients. Because we have an outpatient clinic we see a lot of RSD patients, about 6–7 new ones a week, and we see patients from other clinics in our country. Unfortunately we also see patients who are therapeutically resistant, no therapy possible anymore and we saw 8 of these patients. We opted for amputation because of this and recurrent infections. We know that after amputation the chance of developing RSD in the stump is very high. But we had to do them because otherwise the patients don't leave their house. We always tell the patients what outcome they can expect. Above the knee, the duration of RSD varied from one to ten years – a chronic and severe RSD. Syndromes developed after arthodesis, simple contusion, fracture, sprain, and spontaneously in one patient. After amputation I dissected the tissue and cooled it immediately and investigated the sural nerve, the tibial nerve and the common peroneal nerve. Muscles which I dissected out were gastrocnemius and soleus muscles. The work was done by the research group of neuromuscular disorders at our unversity . . . they looked at these slides. They analyzed it with an open mind.

Slide: Normal man about 40 years, stained for lipofuscein – a product of oxidative stress. We all have them in our body and it increases when you get older. Compared this with slide of patient the same age, and you can see some lipofuscien pigment.

Slide: In muscle of RSD patient you can see a lot of lipofuscein pigment, and it was present in all eight patients. One remarkable finding – that there is oxidative stress present in these patients.

The next surprising finding on electron microscopy. Normal endothelial cell of capillary, but in all RSD patients we find an onion-like structure – a lot of basal membranes. Very new finding, and is described in the diabetic foot. Also, a lot of reasons why this may occur – could be oxidative stress.

What is oxidative stress – is this related to free radical damage? Free radicals react immediately with any substance. They have an important role in arthrosis and ischemia reperfusion, a lot of diseases.

Slide: The nerves did not show any abnormality. Sural nerve showed a light pathology in 4 patients, very mild.

Slide: Free radicals are also important in inflammation, and that's why in the 80s we tried treatment using free radical scavengers. We started the dimethyl sulfoxide (DMSO) application on skin of affected extremity. In one study that was double blind we found that after one week patients had less pain. A study of a colleague with acute RSD demonstrated a significant improvement with DMSO treatment. Another group compared results of DMSO with ismoline IV and showed significant better result in DMSO group. In the Netherlands we treat patients from the beginning with DMSO cream, and then with mannitol, a free radical scavenger, for one week IV.

Slide: In our view the clinical signs and symptoms in the acute phase of RSD are similar to infection. Secondly, you can see on scintigraphy an increased vascular permeability, which you can also see by inflammation. Histology provides findings that may be similar to oxidative stress, and the antioxidant treatment gives good results, indicating there may be an inflammatory response possibly by the pathophysiological mechanism of RSD and as a mediator of free radicals. There are a lot of studies of free radicals but always a combination of interlukeins or with ischemia reperfusion there's an alteration in oxygenation, so there's very little known about what free radicals are doing to humans or animals.

Slide: For this reason we tried to develop an animal model to investigate the effect of free radicals. Using a rat and brought a small artery just above the arteria femoral and placed a catheter around the neck to it's head. In this way the circulation is not altered and we can infuse the rat continuously without altering his system.

Slide: I used debritol hydroperoxide, a free radical, and compared it with the infusion of saline. Saline infusion in this animal did not do anything to the rat. Looked at same signs and symptoms of RSD – measured skin temp, edema, and observed if plantar feet were red or other colors, and walked rats to check function, and performed the same pain test as performed in model of Bennet.

Slide: Found shortly – swollen feet and impaired function and pain tests are positive. Mechanical allodynia, spontaneous pain behavior and allodynia for heat.

Slide: Surprising element, when you look after the beginning of this, and one day after infusion, then disconnected and observed them for 7, 14, days, etc. When we compared the saline infusion, after one day there is no response to frequency, Von Frey filaments, no organic pain sensation in saline infusion. The other group after one day shows an increased response, but in contralateral limb after one week is also showing a withdrawal reaction to the Von Frey filaments. In this model, I also used scintigraphy to see if there was an increased vascular permeability, and indeed it was found, significantly.

Slide: So, perhaps this model may be usable for comparison of acute CRPSI in the future.

We suggest that a regional inflammatory response may be involved as one of the mechanisms in the pathophysiology of RSD. In our opinion, oxygen-derived free radicals may be the possible mediator in this process.

19. Empirical revisions of CRPS criteria

N. Harden

Chicago, IL, USA

We all agree that RSD is not a good name for this syndrome. Thus, the need for the Orlando conference – a think-tank type of conference. This was an invited workshop of the relevant experts of the day, both scientists and clinicians. This Dahlem type conference generated the diagnostic criteria used since then and was an important effort. One of the principal things they tried to accomplish was to create a "big umbrella", to bring most of the people with this syndrome under the diagnostic umbrella. This was crucial at the time. They admitted that we didn't have a lot of mechanistic information, and our charge was to take this set of criteria and to empirically and experimentally validate it over time and improve it. So this is our first stab at an effort to try to improve these criteria a little bit.

We have found several problems with these criteria. E.g. Presence of an initiating noxious event is actually not an absolute criterion if you read very carefully in the IASP book. We do see a lot of spontaneous cases and we should not exclude these, so criterion 1 is not required.

Criterion 2 is necessary, but you'll notice it says "continuing pain, allodynia, hyperalgesia with the pain disproportionate to the inciting event" – in other words they're in pain and no one really understands it on the basis of what has happened to them. That's almost a given if they're coming into our clinics, and is a subjective judgment by the diagnosing clinician.

Criterion 3. This is the most problematic. "Evidence at some time of edema, changes in skin, blood flow, abnormal sudomotor response" – in other words, autonomic disturbance, which we all agree is part of the syndrome. Unfortunately, the way this is worded it allows this to have occurred according the to the patients' observation at any time historically, so it can be entirely subjective. So the patient can say, "I hurt, I was swollen once three months ago," and we make the diagnosis. It's good to have this level of including everyone under "the umbrella", but we need to make this a bit more objective because now it can be based on more objective findings (specificity).

This set of criteria made it for the second edition of the IASP classification of chronic pain syndromes, and everyone is familiar with that. This is probably a document we need to work with, and instead of throwing stones at it we need to work with these editors and help them improve it. It is meant to have a third edition and a fourth edition, etc.; it's like the story of psychiatry that's gone through DSM1, 2, 3 and now 4, and gets better and more validated over time. In the case of CRPS it is our responsibility to validate it scientifically.

We take this charge very seriously in looking at our patients in the clinic. We decided we would not only look at the criteria, but everything else in regard to signs and symptoms mentioned in the reasonable literature. Also, since we've been using these criteria we noticed that there were some things that did not seem to be covered – such as the motor aspects of the syndrome.

Finally, we are actually getting some information about mechanisms, and this information should be changing our thinking about the way we make our diagnosis and clearly should influence the criteria we use to make the diagnosis.

We took a look at the literature and tried to determine all the signs, symptoms and tests mentioned in reference to this syndrome. We didn't exclude any or put these in particular order. We just routinely started collecting these data in patients in whom we'd made the diagnosis of CRPS, based on the criteria from IASP. We took these criteria at face value and made them the gold standard. The details of this have been published in PAIN. The internal validation and external validation of these data are available for your detailed examination. We hope that features of these data will help stir debate so we can talk about modifying the existing criteria and making them better.

There are no real surprises in terms of the signs and symptoms we saw – burning pain, hyperesthesia, hyperalgesia, allodynia. It may be a surprise that we infrequently saw nail and hair changes, but this could be a process of referral bias. There were seven centers involved in this study and we deliberately tried to minimize the bias you usually see with patients referred to academic centers. We had a private practice group, an army physician collecting as well so as not to have only those worst case scenarios that come to my personal clinic – most of my patients actually come to me after having failed at other pain clinics. We won't even talk about the psychosocial issues involved. I do want to point out something here, and that's the weakness which was mentioned frequently by our patients and seen by us. Also, the decreased range of motion, not to mention the tremor and dystonia that was seen. Again, we probably need to be looking at motor changes in our patients as an important part of the syndrome. Also notice that symptoms were recorded more than signs. These are data from 117 patients – we planned to stop at 100, but since we'd started this process at seven centers we closed the first analysis at 117.

One of the ways we looked at the data was factor analysis – a statistical way of trying to see which signs and symptoms naturally group together. The biostatistician tells me we do not have enough patients yet to do a cluster analysis. Factor analysis gave us some very logical categories to think of in terms of diagnostic criteria. Hyperalgesia signs and hyperesthesia symptoms did factor together very strongly. Temperature asymmetry, color change signs and color change symptoms also factor together. Interestingly, edema grouped very strongly with sweating asymmetry. I won't make any physiologic comments on that, but clearly edema and sweating seem to load together quite strongly. Another factor that I'm trying to make a case for including as a criterion are motor signs – decreased range of motion (signs and symptoms), motor dysfunction signs and dystrophic symptoms and signs all factored together as a group.

Another type of analysis is the external validation. We compared the same database to patients with known neuropathic conditions. We only had 43 subjects, but we were trying to see the ability of the CRPS criteria as we knew them to discriminate between known neuropathic conditions – diabetic peripheral neuropathy, post herpetic neuralgia, and carpal tunnel. We found that the criteria from IASP did discriminate well – statistically significant to 0.001. Of course it was very sensitive – we used a scrupulous application of the IASP diagnostic criteria as the gold standard – we found a 0.98 sensitivity. We found a very poor specificity – a 0.36 – so we were only able to accurately make the diagnosis using the IASP taxonomy about 40% of the time.

We went on to create a research-based criteria loaded with these factors and sensitivity/specificity data to see if we could improve the specificity while retaining the good sensitivity, and this is what we found. We picked one of these to analyze that had the highest specificity as we were interested in a research device, something that we could use that would be very specific in terms of bringing people in for study. It required at least two signs and required four symptoms categories. The thing we liked about this formulation was that it retained good sensitivity. You'll notice that depending on how many signs or symptoms you include you can actually set the sensitivity and the specificity within certain parameters. If you just add one sign to a criteria the sensitivity doesn't drop too much and you almost double the specificity. In other words you can set your criteria based on what your interest is. If you interest is medicolegal, you may want to use more specificity; if your interest is patient advocacy you may want more sensitivity. We're not saying which one of these you should select except in the research criteria. All you should do is state exactly what criteria you're using and why.

This is a proposed experimental revision of CRPS diagnostic criteria for research emphasizing while retaining the highest possible sensitivity. 1. continuing pain which is disproportionate to inciting event (we retained that as the first criterion). 2. must meet two or more of the symptom criteria (vasomotor symptoms, sensory symptoms, sudomotor/edema symptoms, and/or motor symptoms); 3. must have two or more signs (vasomotor, sensory, sudomotor/fluid balance and or motor); and this is where you bring in the objectivity. Remember the factor analysis required that we load the sudomotor and the edema together (please see appendix to abstract in booklet).

20. Diagnostic criteria; comments

J. Campbell
Baltimore, MD, USA

When I look at the literature I get the sense that there's a lot of disagreement about these things, so we need a consensus. One thing there is a fairly wide agreement about is that there is not a perfect overlap

between whatever is CRPS and what is SMP – now SMP has the advantage of being an empiric problem, so if we can rely on our test as being highly specific without placebo responses then we can say a patient who has a demonstrated contribution to the pathophysiology by way of the sympathetic nervous system – that that is SMP. That's an empiric designation and does not rely on other disease classification issues. I would submit that there is some proportion of CRPS patients – probably small – that have SMP. At the same time I would submit that there are several patients with SMP that have none of the criteria for CRPS, especially with regard to edema and other "sympathetic dysfunction" manifestations who in fact have SMP – might include patients with nerve injury. They might be others as well. I would draw your attention to this part of the WEN diagram as being a source of patients as well. Another issue is whether there is such a thing as SMP – having agreed that blocking norepinephrine release in the affected tissues given that we can do that or given that we can block the activation of adrenergic receptors by way of giving them an antagonist – are there patients that respond to those interventions. I would say that though we can quibble that with individual criteria there are criticisms that can be posed, when we look in aggregate at the data available to us, the data favoring SMP mechanisms, at least in some patients, is quite substantial.

I thought it might be useful to very quickly run through these – some of this work is not yet published. It's been presented in abstracts, on its way to publication. There is a QST abnormality in these patients – cooling hyperalgesia I believe is a marker for SMP so it does not include all patients with all varieties of hyperalgesia. They can have touch-evoked pain, allodynia to mechanical stimuli, but cooling hyperalgesia I would say is present in a very high percentage of these patients. Phentolamine, I think is a superior test in that it confers some degree of specificity in that it goes after alpha adrenergic receptors. It can be given in a way that obviates the placebo effect – one can relegate a condition such that the placebo effects are very small in the clinical situation – one does that by instructions to the patients. So if you want a placebo effect to be high, 70%, you can do that by how you interact with the patients. If you have a 70% placebo rate it's like having 60-cycle noise in your electrophysiological recordings – you will never establish that aspirin helps pain, or morphine, because your placebo rate is too high. If, however, you establish a neutral environment for the patient, where you say something will be done at a time unknown for you, and the outcome of this test may be that your pain may get worse, get better, or stay the same – and this will not influence your care or our involvement in trying to help you, this is merely a way for us to guide your therapy. When one gives phentolamine under those circumstances, and in particular if the placebo effect is further obviated by giving the drug at a time such that the patient does not know when it happens, placebo problems are largely obviated and constitute a very small issue in doing this test. Lumbar sympathetic ganglion blocks have a number of problems. One is that the anesthetic overlaps with somatics, obviously, but one can really enhance potentially the value of this test by combining it with one other type of intervention, and I'm submitting that this be part of our diagnostic criteria for SMP to improve our specificity. That is, it's work done by Srini Raja, at Hopkins, where norepinephrine is injected in physiological concentrations, into the skin, in patients who are rendered somewhat pain free – much less pain, with a lumbar anesthetic ganglion block, so that's an entry criterion – a response to that kind of clock. Under those situations where there's reduced hyperalgesia the patient receives norepinephrine, but it's done in a blinded fashion so they're getting saline injections intermixed with injections of physiological concentrations of norepinephrine, and we're looking for provocation of pain with the norepinephrine. So that adds further rigor to our establishment of SMP as an important pathophysiological mechanism in-patients. Clonidine can be applied topically to patients, and a remarkable factor is that the cooling hyperalgesia and the touch-provoked pain, this appears in our experience in SMP patients in the area treated with this clonidine patch. So one applies it and then after five days, so there's good loading in the skin, one removes the patch and then again in blinded fashion one can do sensory testing and look for alterations in the cutaneous hyperaglesia in that treated area. Ursula Wesselman, a neurologist at Hopkins, has done this with placebo patches and clonidine patches, and has demonstrated that there's a retreat of the hyperalgesia in that clonidine-treated area. That does not equate to a relief of the overall pain necessarily.

Ultimately, this topical clonidine therapy may evolve into a therapy as creams and ointments that cover a wider area are developed. But this patch test is available for use now. And I would submit that this is a further tool we can use to establish with specificity the presence of SMP. I think the validity of the SMP idea is further substantiated by the marvelous animal model work now available from several laboratories. This work –

we should give credit to Ed Perl – our labs have been able to look at this in a primate model, a Chung model, and nociceptors become catechol-sensitive after injury to a nerve root in the monkey. Finally there is some suggestion – anecdotal reports of response to alpha adrenergic receptor therapy that occurs in certain patients. I think we're confined in our dosing of patients because of the effects of postural hypotension, but regardless of this there are some patients who can tolerate reasonable doses and do respond to alpha adrenergic therapy. We don't see responses to propranolol in these patients, which block beta adrenergic receptors, we don't see prominent responses to other drugs as well. I would say that though anecdotal, these data suggest we're dealing with a specific disorder with regard to SMP by virtue of response to alpha adrenergic blocking therapy.

My experience as a surgeon is similar to what has already been presented with regard to the series reported here.

Parting remarks. Long term we want to do things like Dr. Van der Laan presented – develop models and test them out as hypotheses. With regard to CRPS this is an idiopathic disorder – our job as clinicians is to find definable disorders and refute CRPS – if it is we're stuck with palliative care, opiates, etc. The edema we see is a lymphedema, I think, not venous, no pitting. This might be a hint. The fact that it spreads – and I'm not sure the trauma link – triviality is a powerful hint. Certainly appears to spread in some patients. I'm not at all convinced that it has anything to do with nerves – we've done skin biopsies in a few and haven't seen anything obvious with regard to epidermal innervation. I would suggest that there may be something immune going on – involving cytokines, chemokines, etc. I would also suggest we throw out tests of autonomic dysfunction except in clinics where there are investigative work going on and specific protocols where these tests are used to illuminate mechanisms of CRPS. Triple-phase bone scans really don't help us therapeutically, guanethidine is primitive. . .

Last comment. We should worry about large theories because when I see a patient with CRPS I see as my main mission to disprove that diagnosis, i.e., to try to find another underlying disorder where I know what's going on pathophysiologically.

I'm impressed with the quality of the pictures shown here with regard to the specificity issue. I think the patients with these blown up edematous hands, these are the ones we should restrict for our study, because these probably are patients with CRPS, we're going to be unsuccessful finding another pathophysiology. I would suggest that when we look at mechanism these are the patients we should investigate and try to understand.

21. Diagnostic criteria: comments

B. Boas

Auckland, New Zealand

The single entity still is for some, the sympathetic coupling – at peripheral level, DRG, the nerve, or more central spinal level. And we've become obsessed with the coupling process. But in fact it's probably a multifactorial disorder. And the critical feature of it is that it changes over time – it's dynamic, and we might look at a window at one phase of the disease and then months or years later being so dynamic it's got a different form and a different series of abnormal physiological processes which are manifesting. That makes the diagnosis difficult because we're looking at one little window of time – it's so dynamic that we can't establish any single functional disorder to that sequence. There's no gold standard then that allows us to make this critical diagnosis, and what we've done, as Norman Harden showed, is make the diagnosis and then have a look at all the clinical features and see if we can put that into some sort of constellation. The cluster process that he's seeking to generate is I think the best approach: for us to take this disorder and look at these clusters over time and see if we can generate some evolutionary process and then perhaps out of that evolve back through testing into some generational pathophysiological aspect of it. Then of course we're left with the treatment, but clearly it depends on that sequence of processes. So what I'm going to suggest first is the disorder of pain is complex in each of its processes. Now we understand, and in the definition we have, peripheral nociceptor as the generator that provokes it. But there are other elements and each of these overlap and together form the presentation of pain. And there are about six or seven different elements to this pain in terms of the clinical testing that we undertake. We've heard a lot about central hyperalgesia and windup and we've heard a lot about SMP – I'll put it to you that SMP means stimulus-maintained pain. That stimulus may in part be a sensitivity to noradrenalin, but it may be a sensitivity to hydrogen ions, to bradykinin, to interleukin 6, to leukocyte-inhibiting factor. It may be a stimulated sensitivity to mechanical or thermal stimuli. In other words, SMP may incorporate sympathetically maintained pain but there should be other stimuli as well so that the sympathetic element is but one of a series of sensitization states manifesting peripherally but having a central component and maybe having a coupling component, but this is quite

dynamic, and this total presentation may at some time represent a large bit of this and a little bit of that, etc. But these components may change with the dynamic process of this disorder. So I think the features of pain are not one pathophysiology but a combination of several and we have focused for too long on what might be just one element of this process. That's something that might lend itself to some form of critical testing or evaluation.

Slide: If we're looking at a phenomenological disorder we're applying it solely to the limbs. Biologically that seems extraordinary to me. If there's a disorder just affecting the limbs, then there has to be a clear anatomic and physiological explanation for it. If we're looking at some more generic abnormality I put it to you that there are other analogs of this very same sequence of pathological changes, and some of these analogs, depicted here, all have features that we assign diagnostically to CRPS. Regional pain, vascular, sensory, inflammatory and functional changes. Loin pain hematuria is an extraordinary severe pain in the loin, often with a preliminary painful state that sets it off, it has hematuria, vascular changes, increased blood flow to the area, surrounding inflammation and of course change in renal function. So that to me complies with all the diagnostic criteria of CRPS that is affecting the vessel order. Chronic pelvic pain syndrome – hyperemia in the pelvis of these people with by angiography or by direct vision with laparoscopy – it's quite dramatic, with a lot of pelvic pain, swelling and other features, interstitial cystitis, irritable bladder, bleeding, hemorrhages in bladder wall. Chronic pancreatitis might be an exception in terms of the vascular change, I'm not aware of it, but I'm treating this within the same spectrum of disorders and haven't done a nerve block now in some time. Treating these similarly, as though it has some sensitization state that's been conditioned in these people and sets off the same set of pain disorders.

Correlation of many of these disorders with migraine headaches. The co-association would suggest that within these disorders there's also a surprisingly high incidence of CRPS – or take CRPS and ask them about these symptoms, you'll find that 55% at least will have co-association – with other sensitization state disorders. As though this is not a focal but rather a systemically altered state. I'd like to leave you with that concept ... CRPS is just one manifestation of a certain type of dysfunctional state4.

Slide: Extending that, I'm suggesting that there may be a predisposition state in CRPS, with some patients having these sort of problems, but there's a subgroup of these patients, predominantly female, who are predisposed to having such pains. One of the causes I believe may be apparent within the context of chemical intolerance. Some of you may have noticed the susceptibility of these patients to tricyclic drugs – very sensitive to small doses of tricyclic drugs that literally wipe them out. I suggest this intolerance is because of the changes in descending inhibitory control mechanisms, and that these people have much less in the way of descending inhibitory control and in part this is manifest by the response to drugs that generate that, such as the tricyclics. This is a feature of animal models.

Slide: The manifestations of these disorders in terms of symptoms and signs, and suggest that within these categories – and there are many factors – 40 different signs and symptoms within each of these, and the clustering of these may be important in a better diagnosis. But it might be that each of these elements has a different etiology. So it's linking these processes that make this complex.

Slide: Treatment. Take each of these pain elements and look how we can combine the approaches to therapy. This is just to treat the pain, not the other elements of CRPS... That is to isolate each of these in terms of drugs that act at these sites, and through that process get some potentiation of effect between one mechanistic process and another. What I've done is link some of these – some apply to one or more, but they allow something of a rational way of looking at how you can apply different therapies to each of these pain components. This is the sort of system I try to use and look at these in each patient – sometimes we'll do intravenous type infusions or diagnostic blocks in an attempt to elaborate what might be the relevant contribution of each of these so we can apply therapy in proportion to that contribution – an attempt to simplify and rationalize treatment. Whether it's appropriate or not – that needs testing, but the difficulty we have in the clinical context is an ethical one and a clinical one to meet the patient's need for treatment. To set up control and blind studies is difficult to do in a clinical setting – I think it's one of the failings we all have in trying to come to grips with this subject. The patients' needs take a priority above the science we'd all like to apply to their care. We're limited because of the patient-doctor relationship we're trying to foster.