Theories of Pain: Peripheral and Spinal Cord Mechanisms

The Scientific Basis of Medicine

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<**Professor PD Wall over illustration from Descartes showing classical pain model**>

You are looking here at a 300-year-old diagram from Descartes which shows the classical pain mechanisms and although the labels have been changed, this is the way most of us were taught about pain mechanisms, and it shows essentially three stages: injury, a peripheral nerve detecting the presence of injury and conducting it into the central nervous system; and then a conduction pathway along the spinal cord and into the brain, a pain centre. Now, what's wrong with such a rather beautifully elegant, simple mechanism? Well, there are three things wrong.

<**Wall to camera**>

And the first one is that your own experience of your own pain, and pain in your patients, simply doesn't fit a simple stimulus response mechanism of this kind. There are always present phenomena such as the bizarre relationship between the

stimulus and the response: in the extreme, gross injuries without pain or extreme pain without any appearance of injury and, in fact, any particular pain somewhere in between that. In addition, there are phenomena on the side such as hyperaesthesia, where very light stimuli induce pain, such as referred pain where there is not only the pain mislocated but stimuli in the referred region adding to the pain, so that to fit any particular pain to this simple model one has to add these ad hoc mechanisms over and over again. That isn't very satisfactory.

Now, the second thing that's wrong with this diagram is that it simply doesn't fit what has been found with anatomy, physiology and pharmacology. And the third thing wrong with the diagram is that it contains an inherent pessimism about it, because what are you going to do about a pain? All you can do if this mechanism is right is either try to prevent the impulses being generated in the first place, or to block or cut the pathway either by surgery or by chemistry. So that one is left with very few possible therapies.

Now, let us take my second point that the anatomy and physiology doesn't fit and go now to analyse, bit by bit, what is actually found in this pathway, and we'll turn now to a simplified diagram of the first part.

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<**Wall over diagram showing the most basic model of a pain pathway**>

Here you are seeing the minimum two components that must exist. A peripheral nerve fibre that's detecting the presence of injury, projecting onto a cell in the central nervous system. Let's ask first what has been found out about these peripheral nerve fibres? They really do exist in a very impressive and highly specific fashion, that is to say, there are small myelinated and unmyelinated fibres which respond only in the presence of injury. Now, that far, the original diagram has been fully justified – one has to add some modifications, for example, while injury is necessary to fire the fibres, other factors such as the presence of prostaglandins modify the sensitivity of the fibres so that the threshold is not really fixed throughout the life of the person,

and injury of the nerve fibres, or sickness of the nerve fibres, further modifies them. However, we do have this basic simple input pattern which really exists and all of the tests in man and animals have shown that.

<**Wall, seated, refers to series of photographs and diagrams showing models of pain pathways on display board to his left**>

Now let's move on to ask, well, where does that type of nerve fibre end in the central nervous system? And let's look quickly at some diagrams. Here is a picture of half of the spinal cord, here are the dorsal roots coming in, which are delivering those fibres, which are going to terminate somewhere in here, in the grey matter. And let's move to a simplification of that diagram, of that photograph. Here then are the cells sitting, actually in rather beautifully laminated layers in the dorsal part of the spinal cord, and the afferents come in here, terminate on cells actually in various regions. Now, let's have a look at the anatomy of those cells.

Now, here is a picture from Cahal, showing the sort of thing that one would really like to see. That is to say, here is the dorsal root bringing in the afferent fibres, here are cells actually in the marginal layer receiving those sensory fibres, and this is really almost designed to look like that Descartes picture brought up to date. In other words, a cell dominated by a particular type of peripheral nerve fibre. Now this really is a gross cartoon, a gross oversimplification of matters because not only these cells but all of the deeper cells have really a somewhat more complex anatomy.

And here's a diagram of this. Here are the nerve fibres arriving from the periphery, here is an example of one of the types of nerve cell that then projects towards the head. But, in addition to the arriving nerve impulses and the transmitting nerve cells, there are many, many other cells sitting around. In this case the cells of substantia gelatinosa: very small cells which don't project at all towards the brain or to any other structures and are in a perfect position to control and modulate the transfer of impulses from here to there. Alright so let us ask then, if we probe around in the spinal cord looking for cells of this variety and asking each one "do you respond to injury?" Do we find such cells? Well, the answer is yes. As I said before, the spinal

cord is made up of a series of rather spectacularly organised laminae, running from the dorsal posterior part to the ventral anterior part here, and in a number of these laminae, particularly in this first little lamina up here, this lamina in the middle of the dorsal horn, there are cells which signal and transmit the presence of injury in a specific, carefully localised peripheral part. And let's have a look at the firing of one of those cells.

Here is a diagram, made from a recording from a single cell, actually this one is in lamina 5, that middle region there, and we're looking here at a diagram with time, going from here to here, this is 2 ½ minutes from there to there, and each dot is a single nerve impulse in a single cell and what happened was this. At this point here, you see the cell was not firing up to this point, at this point a clip was put, a haemostat was put, crushing the skin in the centre of the receptor field of this cell and you see the cell begins to fire immediately and the firing goes on. And at this point the clip was removed and the cell goes down to only firing very small amounts.

And if we look at a much more common type of cell, which you see here. Here, the same arrangement, this is time from here to here, several minutes, here nothing had been done, the cell was ticking over at a very low frequency. Here the injury was applied and the cell begins firing at very high frequency and then peters off to, still, a very high frequency, lots of nerve impulses. At this point, the clip is removed but, of course, the tissue remains damaged. And so, after the injury, that remaining damage is still creating firing which will go on for many minutes or hours.

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<**Wall to camera**>

Now, fine, we have now located then, and examined, cells in many parts of the spinal cord and labelled not one type of cell but many types of cell that are responding in injury. Now you'll remember from the original diagram, and from one's intuitive way of thinking, that that should be all that the cell does, it really shouldn't be responding to

anything else, it should be purely taking those messages and transmitting them on. Now, let us ask if that really is the case. And for this, let me now show you the second diagram to which we have to add a first additional component.

<**Wall over previous diagram of basic pain model, with addition. Then to camera**>

Here you are seeing the original and the addition appearing now. The addition is this: as the injury signals come in and fire off the transmitting cell, they also fire off side circuits which add to the message. You will see that this produces an amplifying factor, and perhaps you don't think, quite rightly, that this is a very profound modification, it does help to explain the ringing of the pain after a single brief injury or a single brief electric shock. It can be of some very considerable importance to explain some of the pathologies which occur after denervation, after rhizotomy, and injuries of that variety. So that here we've got a first modification – the input signal is amplified so that the output signal may be quite considerably larger than the input. Alright, not a very major modification, quite acceptable.

But now let us ask a much more fundamental question, and here we need to ask: do non-injury signals influence this cell in any way? And here we come across the first really surprising fact and that is that many of these cells are actually also excited by large, low-threshold afferents. This is shown in the next diagram.

<**Wall over diagram illustrating pattern of referred pain**>

Now, this is a physiological fact that our injury-detecting cells are also excited by light stimuli in a different place. Now this also fits in with your experience. This is, as I said, a physiological fact, but it helps explain the hyperaesthesias, why it is that in the presence of injury in one place, a distant region can be tender, by which one means that light touch increases the pain – why should that be? Well, it turns out that part of the explanation occurs immediately at the first synapse inside the spinal cord, that a whole class of these cells has a convergence on them from both exciting – the main excitation comes from the injury input, the small fibres – but topping it up; adding to it

are inputs from the large fibres. In the case of regions where you have referred pain, this fits exactly, that is to say, input from the abdominal region, from viscera within the abdomen; it turns out that all of the receiving cells also receive a minor but excitatory input from the skin on the abdomen and this, of course, fits exactly your clinical observation that an appendicitis, let us say, is incorrectly referred by the patient to the surface of the abdominal wall, not correctly located as to where the appendix is. And if you probe that region and gently press on it, you increase the pain. Here apparently is the mechanism for that type of hyperaesthesia and referred pain.

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<**Wall to camera, then over previous diagram of basic pain model with further addition**>

Now, again this is perhaps surprising but quite acceptable. It breaks into the classical, specific, messenger boy, fire alarm pathway and says that you've already got additions to the pathway even by the first central cell. But let us ask: is that all that those light touch, low threshold afferents do to these cells? Well, no it isn't. And now we have to add the next component, that is, an inhibitory one. Let me show this.

We have our original parts but it turns out now, in the case of all the cells that have been detected, that of course they are fired, they are excited by the small injury-detecting afferents, but they are all also inhibited by the low threshold afferents coming in. Now here we're getting a long way away from the classical model, but we're approaching reality in a number of ways. You will see now that you have that filled-in cell on the left which is producing some inhibition. It means that the firing of the cell is under a balance – one lot of inputs tending to make it fire and even exaggerate that firing, the other lot of inputs tending to turn it off. Now that applies to all biological systems of any importance; they are always under a balance of this sort, and here we have an example of this type of inhibition from the dark cells, excitation from the light cells, intruding on the through pathway.

<**Wall to camera**>

Now, this has a number of strong practical consequences. What the brain knows is what is transmitted to it and now we are seeing that what is transmitted to it is nerve impulses, of course, which would say injury occurs. But there are peripheral mechanisms which can both increase and decrease that signal. Now, does that have any practical consequences? Well, even on the simplest level, of course, in the presence of pain one does very odd things like scratching and rubbing – what is that all about? Why should one do such a curious manoeuvre? A suggestion is that even such a simple manoeuvre as that is, in fact, sending in these impulses over the larger afferents and partially turning off the system. Now, in some people with very severe pains, this idea has produced an extremely successful therapy. The therapy is to intentionally increase the barrage in the large afferent fibres. The way in which that is done is by electrical stimulation of the peripheral nerves which fortunately happen to respond most easily to electric currents. So as you gradually increase the strength of electrical stimulation you increase first the barrage of these large afferent fibres. And behaviourally, and particularly in certain diseases of damaged peripheral nerve, produce a very remarkable readjustment of the balance. So that the patient with very intense hyperaesthesia, due to a failure of the inhibitory mechanisms, may have the inhibitory mechanisms reinstituted.

That is shown most satisfactorily in a type of post-hepatic neuralgia where the pain referred to the skin, where light brushing produces intense discomfort and pain, electrical stimulation drops the excitability of the system towards normal and light stimuli no longer produce pain.

Fine. Now you can see we are moving at some distance from our original model. We are adding more components to the physiology, but we are also beginning to approach something which begins to allow us to talk about actual clinical phenomena of pain and, particularly, the troublesome chronic pains and the deviations from the expected situation – the expected situation where you stick in a pin, feel some pain and that seems to be all there is to it. As you know, even a case of, let's say, post-operative pain, and certainly any of the chronic pains to do with peripheral nerve

injury, peripheral nerve damage, deviate more and more wildly from that expected, simple, stick-in-a-pin feel-pain situation.

Now, do we have to add any more components? So far we've only been talking about the first central cells and how they handle the impulses coming in from the periphery. But we have to add a new component which you will see in the next diagram.

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<**Wall to camera, then over previous diagram of basic pain model with further addition**>

And the new component is that impulses descend from the head; there are descending systems of a very powerful variety which tend to drop the excitability of our transmitting system – you may be relieved to hear that this is the last component that I'm going to add here – but in terms of effectiveness and the present interest in future therapy, or even present therapy, this one turns out to be very interesting. That is to say, the brain itself is sending orders down to this first entry point, the gate of entry into the central nervous system, orders which essentially decide on the excitability of the system. Now, these come from a number of sources, a number of surprising sources, even the pyramidal tract contributes some of these orders so that, not too surprising, that movement, or the orders for movement, are themselves associated with a readjustment of the pain pathways. A well-known phenomenon that if you can persuade a patient to move is very often, quite apart from the distraction effect, accompanied by a decrease of pain. A curious balance now between the tendency of the movement to increase the injury signals from the periphery and the tendency of the movement to cut down the signals that are transmitted in the central nervous system.

Now one of the reasons why this new pathway, which you see on the left, is of great interest is that people are now searching for the origin of those descending pathways. One of them has been found to originate in the midbrain and this is

sufficiently powerful and sufficiently impressive that quite a number of patients, both in this country and in the United States, are now having localised electrical stimulation with electrodes in the periaqueductal grey region of the midbrain which generates, indirectly, one of these descending inhibitory mechanisms. These patients are experiencing a most satisfactory analgesia without any other apparent disturbance either of their sensory system or their motor system or their mood or anything of that sort.

<**Wall to camera**>

Now, a second reason why this descending pathway is of great interest is that it appears to have something to do with the action of the narcotics. The narcotics, obviously the most spectacular of the analgesic agents, how do they work? Well, in animal studies it turns out that it looks as though narcotics (morphine and, in fact, the entire group of narcotics) are somehow stimulating this descending pathway that I've been talking about, originating in the midbrain. Now, of course the narcotics are doing a lot of other things, both in the periphery, in the gut, on other cells like the respiratory cells and on cells to do with mood. But, in addition, we've got a highly specific, morphine-like effect on these cells.

Now, the story becomes even more fascinating because one asks why should it be that an extract of poppy or a product of chemical factories should have such a specific action on such a small group of cells? The answer appears to be a very fascinating one. It seems that these cells are normally producing a narcotic-like substance and there is a great debate going on at the present time, whether we are really either continually generating inside our heads, or under specific circumstances, generating narcotic-like substances called endorphins which may be actually nerve transmitters which, and one of the things these nerve transmitters are doing is triggering off a descending nerve pathway which, in turn, inhibits the ascending pathway. Now this is very much under debate at the present time but the evidence is really very powerful, so that the analgesic effect of the morphine / pethidine, this whole family of narcotics, may be because they are imitating an existing natural

transmitter and simply increasing the activity of a pathway which is normally not very active.

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Now, let us just review, by going back to our original model, what we have added to this classical pathway.

<**Wall over earlier illustration from Descartes showing classical pain model**>

I have spoken and said that of course this classical pathway exists, it has to exist, and in fact, in the periphery, a model, a picture of this sort is really almost 100% justified. The most detailed studies of looking at single fibres show that yes, there are single axons detecting the presence of injury in specifically localised places. Where the model breaks down is as soon as you get into the spinal cord or, of course, for the face, into the 5th nerve nucleus. Here we find cells driven by these specific afferents and, in fact, the message that's being transmitted to the head being amplified. Fine, that's a minor modification although one of interest. But we find that these central cells have convergences on them, convergences from non-injury detecting fibres and those convergences, some of them exaggerate the message and some of them turn off the message and this gives a chance to think of explanations for some of the curious pains and to consider possible therapies. And the final modification to the diagram is that all of the transmission pathways are, in fact, under intense control from messages coming down from the head which, again, offers an explanation partly for the variability of signal to response and the effect of attitude, etc., and, as we have said, opens up the possibility of certain therapies like neurosurgical implantation of electrodes and the possibility that the explanation of narcotics' action on pain is, in part, that they are themselves triggering a descending control mechanism which prevents or reduces the afferent volley.

<**End credits**>