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Future Trends in Pain Research

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Future trends in pain research

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In the future we shall need to modify the classical view that nerve impulses which signal the presence of injury are reliably transmitted by specified and automatic relay cells. We must investigate at least four different modifying mechanisms that are likely to generate chronic intractable pains.

(1) With a latency of *milliseconds*, combinations of afferent signals and of descending controls operate a rapid and powerful gate control.

(2) With a latency of *minutes*, impulses in C fibres change the excitability of peripheral endings and of spinal cord circuits.

(3) With a latency of *days*, chemical transport in C fibres from areas of damage further modifies cord connectivity with a disappearance of inhibitions and an expansion of receptive fields.

(4) With a latency of *weeks and months*, anatomical degeneration produces secondary changes in deafferented cells with atrophy, sprouting and abnormal firing patterns.

Introduction

To guess at the future, it is necessary first to define the present state of our understanding and of the nature of the unsolved problems. Tissue damage produces global changes in the entire organism with changes in ways of thinking, feeling and behaving but I concentrate here on the more easily analysed changes in the periphery and in the spinal cord. We are now in a transitional period, rejecting the old views of a hard wired system that reliably reported the presence of injury and evoked pain. Instead we are moving into a period of appreciation of a subtle biological system that recognizes the presence of injury in the context of the overall situation of the victim and produces a series of responses relevant to recovery (Wall 1979).

1. Present knowledge of the mechanisms of the relation of pain to tissue damage

(*a*) *Threshold and amplitude*

Thanks to the remarkable developments of human neuronography reviewed here by Torebjörk and elsewhere (Wall & McMahon 1984), we can now relate the report of trained subjects' pain to the firing of their afferent fibres. For Aδ fibres, Adriaensen *et al.* (1983) report that von Frey hairs sufficient to stimulate high threshold mechanoreceptors do not evoke pain. For chemical stimuli there is a 'rough correlation' between firing and sensation. Heating to 44.5 °C produced firing in some fibres but no pain. At 45.4 °C, all units fired but only 20% of the stimuli were painful. For temperature stimulation of C fibres, Torebjörk *et al.* (1984) conclude that spatial summation of activity in many C fibres was necessary before pain was sensed, and that pain magnitude was more closely related to a population of C nociceptors than to activity in individual nociceptors. This conclusion exactly agrees with an earlier study of Gybels *et al.*

(1979) who state 'Subjective ratings give a better estimation of stimulus size than did the discharge rates of the individual C fibres under study'. In other words, pain threshold and amplitude are not determined by the presence or absence of activity in a particular class of peripheral afferents. Spatial and temporal summation and controlled thresholds of c.n.s. cells decide when pain is triggered. The same conclusion is reached for visceral afferents (Malliani *et al.* 1984).

Even more interesting is the relation of pain evoked by different stimuli to firing in afferents. Van Hees & Gybels (1981) found that pressure stimuli which evoked 10 Hz responses in C fibres was not necessarily painful while temperature stimuli producing 0.4 Hz responses were painful in 86% of the trials. This marked difference between pressure and temperature responses is predicted by the gate control theory (Melzack & Wall 1965) since the pressure stimulus will also activate low threshold mechanoreceptors, which will have an inhibitory effect (Wall 1964). Moving from trained subjects to patients admitted to hospital with severe injuries, 40% noticed no pain at the time of the injury of which they were fully aware, 40% had more pain than was expected and only 20% reported the expected pain (Melzack *et al.* 1982). In summary, the identification of pain is not a property produced by single fibres but depends on the ability of the c.n.s. to extract information from the overall afferent barrage.

(*b*) *Modality*

Humans cannot differentiate between punctate cold or hot or mechanical injuries (Chery Croze & Duclaux 1980) or between different types of chemical stimuli (Ong *et al.* 1980) in spite of the fact that these generate very different afferent barrages. A 43 °C probe on skin evokes pain if it is 1–5 mm diam., and pleasant warmth at 20 mm diam. (Melzack *et al.* 1962). A sharp pencil pressed into the finger tip evokes a sensation of punctate pain but produces a wide cone of indentation within which Pacinian corpuscles respond to 8 μm of indentation, rapidly adapting mechanoreceptors to 10 μm and slowly adapting mechanoreceptors to 50–200 μm (Vallbo & Johannsen 1976). Evidently the c.n.s. can abstract identical sensations from different afferent barrages or different sensations when the same type of fibre responds in different numbers.

(*c*) *Time course*

When skin is heated to 46.5 °C for 15 s or firmly pinched, Aδ fibres fire for 5 s and then become silent or fire at a low frequency. As the rate of firing decreases, the subject reports the onset of pain (Adriaensen *et al.* 1983; Handwerker 1984). C fibres show a similar mismatch of firing in relation to the time of pain onset (Lamotte *et al.* 1982). When the stimulus is removed, firing ceases abruptly but pain continues and even augments. It is again evident that c.n.s. factors must determine this aspect of sensation.

(*d*) *Location*

Punctate stimuli on fingers are located with an average error of 3–4 mm and 5–7 mm on the palm (Hamburger 1980). More crucial for clinical problems is the fact that local skin injury is followed by a spread of sensitivity peaking after 15–20 min (Lewis 1942), whereas a transient noxious stimulus to deep tissue produces local pain within seconds but referred pain at a distance, which becomes maximal at 2 min, and hyperalgesia delayed by 5 min or more, which can persist for hours (Hockaday & Whitty 1967). These shifts of location and of sensitivity signal the existence of a reacting pain-producing system that is not to be explained by fixed properties

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of either the peripheral or the central nervous system. They lead us to a consideration of the problems for the future.

2. The nature of unsolved problems

The practical clinical problems of acute pain of sudden onset and brief duration have been admirably solved over the past hundred years particularly by the anaesthetists even if one does not understand the mechanisms by which their therapies work. Unfortunately, this success is accompanied by a miserable failure to resolve many of the problems of chronic pain where even the most enthusiastic clinician admits to only partial, often temporary, success of his favourite therapies, and to mystification as to the origin of his patients suffering. For example, the regrettably common condition of phantom and stump pain in amputees is currently treated by 41 different types of therapy, none of them reliably effective (Sherman *et al.* 1980). Not only do the therapies fail but the explanations of cause based on classical specificity theory fail equally. The most conservative approach to chronic pain would be to suggest that it is simply a prolongation of acute pain. This approach does not explain the observed phenomena. It appears instead that the peripheral and central nervous systems undergo a series of sequential changes so that impulses are routed and processed in different ways as time passes. It is to this progressive plasticity to which we must now pay attention.

I have described the present state of knowledge in a somewhat unusual way to emphasize the possibility of change even in the normal mechanisms tested in the laboratory. We have seen that threshold, amplitude, modality, time course and location are not determined by rigid specific systems. Each of these aspects of sensation does not depend simply on the presence of some specified afferent barrage but also on the setting of central mechanisms that abstract these properties from the afferent barrage. The characteristics of chronic pains emphasize the change of sensitivity so that threshold is changed to produce allodynia, hyperpathia or even pain with no stimulus. Tenderness represents a shift of modality so that innocuous stimuli to normal tissue evoke pain. Time course and location are disturbed with delay, overshoot, ringing and radiation, characteristic of so many chronic pain states. At least four time epochs within which pain mechanisms change in response to injury can be identified.

3. Plasticity within seconds: the gate control

It is now generally agreed that impulses in nociceptive afferents arriving at the first central synapse are not reliably automatically transmitted with a fixed gain to excite central cells. This gate control is the subject of a number of the accompanying papers and for that reason will be discussed here very briefly. The basic components of this gate control are (figure 1): (1) cells receiving nociceptive inputs modulated by inhibitory and excitatory local interneurons; (2) convergent inputs from other afferents, which influence excitability; (3) descending controls from the brain. Clearly much remains to be learnt of this system; the identification of the interneurons, the origin of the controls, the chemistry of the synapses and above all the actual circumstances under which the controls operate. It is important to realize that this gate system is not simply a gain control since modality itself is under control (Wall 1967) and the organization of receptive fields is changed (Hillman & Wall 1969). This system is capable of rapid shift to extract from the afferent barrage that information required by the biological needs

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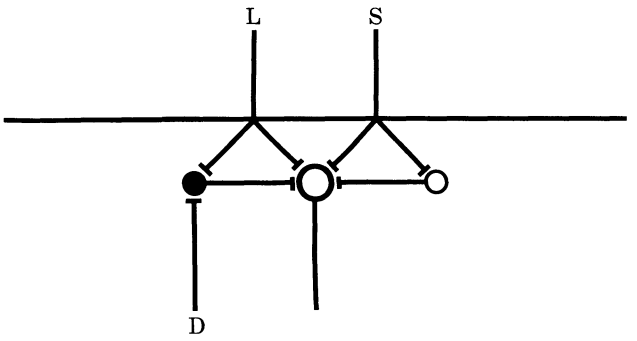

FIGURE 1. Basic components of the gate control. (1) Cells excited by nociceptive inputs (S) flanked by excitatory (clear circle) and inhibitory (filled circle) interneurons. (2) Convergent inputs from afferents signalling innocuous events (L) activate inhibitory interneurons. In some cells, these large afferents (L) also excite the cells receiving nociceptive afferents to produce wide dynamic range cells. (3) Descending control systems from the brain (D) may activate inhibitory neurons. This diagram is intended only to illustrate the direction of effects. It should not be taken to imply presynaptic or postsynaptic mechanisms nor should it be taken to imply only monosynaptic pathways.

of the moment. The speed of the system is shown by the peaking of afferent inhibition within 20 ms of arrival of the afferents impulses and a rapid fading even after 15 min of stimulation (Chung *et al.* 1984). Similarly, descending inhibitory volleys have a rapid onset and decline (Engberg *et al.* 1968). However, we knew from our beginning of transcutaneous nerve stimulation (t.n.s.) (Wall & Sweet 1967) that there were also longer-term effects since four of our eight patients had pain relief lasting more than 30 min after only 2 min of Aβ afferent stimulation. We now turn to these longer onset and duration changes.

4. Plasticity within minutes: central changes triggered by C afferent impulses

After tissue damage a series of local changes of nerve sensitivity occurs in the periphery and there is an important neural component (reviewed by Lembeck & Gamse 1982). Here I wish to emphasize that there are also central changes triggered by peripheral damage. For example, Woolf (1983) showed that the flexor reflex in the decerebrate spinal rat is greatly exaggerated by thermal injury and that part of this has to be attributed to spinal cord changes. Thinking of the common experience that minor deep injuries to a limb result in widespread and prolonged tenderness while equivalent cutaneous injuries result in more spatially and temporally restricted tenderness, we decided to compare the central effects of muscle versus cutaneous afferents (Wall & Woolf 1984) (figure 2). Twenty conditioning stimuli at C fibre strength in the sural cutaneous nerve at 1 Hz produced a marked increase in the flexor reflex lasting up to 10 min. However, if the same type of conditioning stimulus originates from a muscle nerve the flexor reflex is enhanced for up to 90 min. Brief tetanic contraction of muscle fibres or nerve section is sufficient to trigger similar prolonged changes. A related phenomenon has been observed in lamina 1 cells when punctate skin burns were placed outside the cells receptive field (McMahon & Wall 1984). After 10–15 min the excitability of the cell increased and the receptive field of the cell moved to incorporate the area of injury.

C fibre activity is required to trigger these central changes since they only occur if the conditioning stimuli activate C fibres. Furthermore, they do not occur if the conditioning nerve has been treated with capsaicin, a selective C fibre neurotoxin. It is important to stress that

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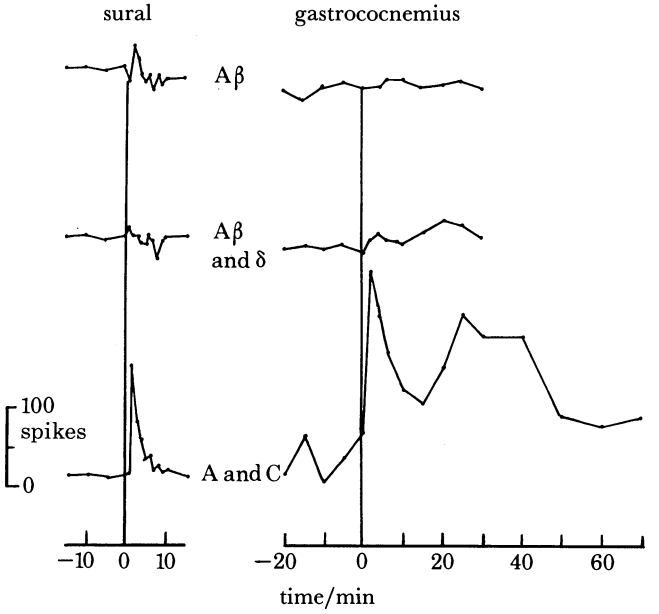

FIGURE 2. Plasticity within minutes: central changes triggered by C afferents. The flexion reflex was measured by recording the discharge of four motor neurons to posterior biceps femoris in a decerebrate spinal rat. The reflex was evoked at the indicated times by a 3 s pinch to contralateral toes. The total number of spikes in the reflex were recorded, scale at bottom left. At time 0, a 20 s, 1 Hz, conditioning stimulus was applied at the indicated strength to either the sural nerve or to the nerve to gastrocnemius. Conditioning stimuli to myelinated fibres produced minimal long-term changes in the height of the flexion reflex. However, when C fibres were included in the conditioning stimulus, the sural conditioning stimulus produced an enhanced reflex for less than 10 min. When the same A and C conditioning stimulus was applied to the nerve to gastrocnemius, there was a marked increase of the reflex for over 60 min.

although triggered by C fibres, the change is not sustained by the continuation of the triggering barrage because local anaesthesia of the conditioning nerve fails to abolish the central change once established. These changes may represent a model for the central component of the tenderness which follows injury and will need future study. They are the consequence of activity in C nociceptors not shared by the fast Aδ nociceptors. Since they are slow in onset, the slow conduction velocity of the C fibres no longer matters and we can propose one reason for the existence of the two families of nociceptors. The slow onset prolonged action may suggest a different chemistry of synaptic transmission and a possible function for peptides that characterize the unmyelinated afferents.

5. PLASTICITY WITHIN DAYS: CENTRAL CHANGES PRODUCED BY TRANSPORT IN C FIBRES

Tissue damage inevitably involves destruction of nerve fibres which then emit local sprouts. The physiological properties of these growing sprouts differ from normal mature membrane (Wall & Gutnick 1974). They become spontaneously active, mechanosensitive and are excited by an α action of noradrenaline. Important as these peripheral changes are, I shall concentrate here on a cascade of changes which sweep centrally from the cut ends of axons. The dorsal root ganglion cells change chemically and become spontaneously active and mechanosensitive (Wall & Devor 1983). Central to these cells, the terminals of C afferents change their chemistry and morphology and a series of physiological changes occur within the cord (reviewed by Wall

1984). The C fibre central terminals change their peptide content and, while still capable of exciting central cells, they no longer evoke the prolonged sensitization discussed in §4. Cut A fibres can no longer evoke dorsal root potentials or primary afferent depolarization (figure 3 (B)). Inhibitory mechanisms normally evoked by afferent volleys in the cord fail to occur and excitability rises. The receptive fields of cells which have lost their afferent drive change so that they respond to nearby intact nerves (figure 3 (A)). The latency of such changes in rat cord after sciatic nerve section is more than 3 days.

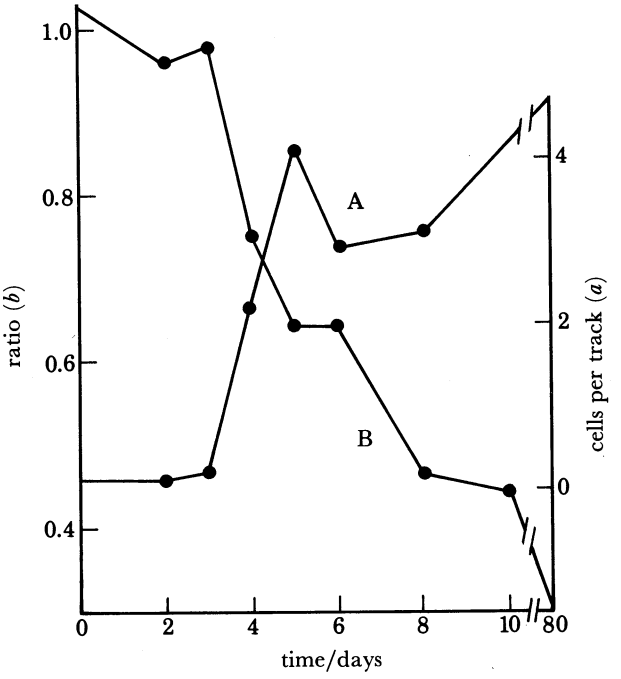

FIGURE 3. Plasticity within days: central changes produced by transport in C fibres. (a) Expansion of receptive fields of medial dorsal horn cells following section of the saphenous and sciatic nerves in the rat. During the first 3 days after nerve section, the medial dorsal horn which normally subserves the foot contained very few cells with peripheral receptive fields. From 4 days onwards, cells with proximal receptive fields began to be recorded in the area where cells previously responded to the now denervated foot. The scale on the right shows the average number of cells recorded in each microelectrode track. (Redrawn from figure 3 in Devor & Wall 1981.) (b) The decline of dorsal root potential (d.r.p.) evoked by stimulation of the sciatic nerve at the indicated times after sciatic nerve section. The dorsal root potential was recorded in rats on the L5 dorsal root after maximal stimulation of the cut sciatic nerve. The scale on the left shows the ratio of the height of the d.r.p. evoked from the chronically cut nerve over that produced on the opposite side by stimulation of the acutely cut sciatic. A marked decline begins 3 days after nerve section. (Redrawn from figure 7 in Wall & Devor 1981.)

The mechanism by which these central changes occur is clearly of great importance for understanding chronic states. Chronic blockade of nerve impulses by tetrodotoxin does not produce them. Crush produces complete peripheral degeneration but fails to induce most of the central changes. There is no evidence of anatomical sprouting of intact afferents to occupy the central territory vacated by peripherally cut axons. Poisoning of C fibres by capsaicin is sufficient to induce many of the central alterations of A fibre connectivity. Bathing the cut end of the nerve with a steady supply of nerve growth factor (NGF) decreases at least three of the effects of nerve section; peptide decrease, primary afferent depolarization (p.a.d.) decrease and receptive field (RF) expansion (Fitzgerald *et al.* 1984).

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It is clear that a message informs the spinal cord that peripheral axons have been cut. The latency and other properties suggest that chemical transport is involved. The fact that local single nerve adult capsaicin mimics many of the central effects of whole nerve section suggests transport in C fibres as the message carrier. The message could be the failure of arrival of a normal compound such as NGF but it is then difficult to understand why crush fails to elicit the effect. An alternative is that C fibres pick up and transport abnormal chemicals from the region of injury and that these induce the central changes. In the absence of any signs of morphological expansion in afferent innervation, the expanded RFs seem best explained by the unmasking of normally ineffective inputs which become effective either because of the loss of inhibitions or because of increased postsynaptic excitability. Whatever may be the mechanism, it is clear that peripheral damage induces alterations of central connections so that part of the problem shifts to the central nervous system away from the initial site of damage. If successful peripheral regeneration occurs, the novel connectivity reverts to the normal, but where regeneration cannot occur as in amputees or fails as in causalgia the central reconnections remain. Their prevention or cure is a major challenge for the future.

6. Plasticity within weeks: atrophy and late consequences

We know least of all about these late anatomical and functional changes although they are discussed in this symposium by G. Guilbaud. Animal models are often studied for too short a time for delayed changes to become apparent and detailed follow-up studies of human patients are rare. In 1970 Grant reported transganglionic degeneration of dorsal root afferents after section of peripheral axons, and many such reports have appeared since. Some afferent fibres die.

Davis *et al.* (1978) followed the decline in area of compound action potentials in cut cat peripheral nerve (figure 4*a*), as did Devor & Wall in rat nerve (1981). This decrease begins at about 2 weeks but continues for at least 12 weeks. More direct evidence comes from Ygge & Aldskogius (1984) who show disappearance of 25% of dorsal root ganglion cells in rats by 3 weeks after intercostal nerve section (figure 4*b*). It is apparent that the physiological and chemical changes discussed in phase 3 may extend and mix with the later degenerative changes of this phase. Examination of spinal cords some months after root section shows a progressive atrophy of dorsal horn, suggesting postsynaptic changes beyond the obvious change produced by degeneration of afferents (Basbaum & Wall 1976). Peripheral damage may eventually produce central irreversible changes of deafferentation and consequent atrophy of central cells, which will perpetuate the abnormality of transmission.

7. The future consequences of the recognition of plasticity in afferent pathways

It no longer makes sense to speak of a single pain mechanism as though it were a fixed set of cells with only the gain under control. Observed clinical signs and symptoms and the physiology, anatomy and chemistry of the nerve cells show that the system changes in time after injury. Very important changes occur in the periphery but, at each stage, it is crucial to recognize that central changes are also in progress. These central changes produce new ways of handling afferent signals whether they originate from the region of damage or from nearby intact structures. These progressive reactions may provide adaptive forms of behaviour with a reorganization of sensory and motor systems to optimize the chance of recovery. Unfortunately,

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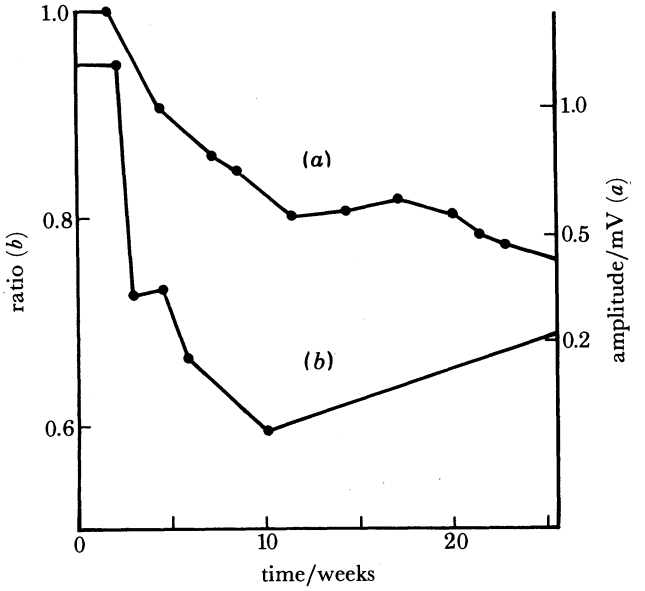

FIGURE 4. Plasticity within weeks: atrophy and late consequences. (a) Amplitude of the compound action potential evoked on the cut sciatic nerve by maximal stimulation of the tibial nerve, which had been severed peripheral to the stimulating electrodes at the indicated times. Scale on the right is the amplitude in millivolts. (Redrawn from figure 3 in Davis *et al.* 1979.) (b) Numbers of rat thoracic dorsal root ganglion cells after different post-operative survivals following section of intercostal nerves. The scale on the left shows the ratio of numbers of cells on the operated side over those counted in the ganglia from the same segments on the intact side. (Plotted from table 2 in Ygge & Aldskogius 1984.)

these reactions may also perpetuate a stable maladaptive pathological state. It appears that the unmyelinated fibres are particularly important in guiding these delayed reactions. The second phase, triggered by afferents in unmyelinated afferents, raises the question of early treatment and of analysis of the chemistry of the prolonged effects. The third and fourth phases, with clues that transport mechanisms may be involved, call for an identification of the messenger chemicals transported by the fibres and investigation of the action of transport manipulation on the development of these disastrous phases, which characterize the intractable aspects of chronic pain.

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