

ANESTHESIOLOGY

The Journal of

THE AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INC.

Volume 12

JANUARY, 1951

Number 1

THE PHYSIOLOGY OF PAIN: ABNORMAL NEURON STATES IN CAUSALGIA AND RELATED PHENOMENA *

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Received for publication May 22, 1950

THE physiology of pain is too broad for this brief analysis; by pointing toward the problem of causalgia, however, the most significant aspects of the larger subject may come into focus. It is encouraging that purely physiologic considerations have led to an interpretation very close to that reached by Livingston (1) from clinical experience.

In the space available, one must necessarily omit much highly relevant material. On the problem of the periphery in pain mechanisms, for example, I can merely state some facts that seem established. There are two types of nerve fibers that carry pain messages centrally: the more rapid delta fibers, about one third of the A elevation and conducting about 20 m. per second, and the very slow, nonmedullated C fibers, perhaps four times as numerous as the A group and conducting only 2 m. per second (2). The latter are particularly concerned with the burning pain associated with causalgia and are often called protopathic. Each pain fiber has a peripheral branching network of its own which may serve an area of several square centimeters, and the separate terminal fibers may interlace; but they do not form a continuum with each other, as had been thought. The separate twigs of one fiber, or of more than one, may interact in the periphery under certain conditions, as in antidromic effects, H substance release, spreading hyperalgesia or, in one fiber, even in normal function (3). The autonomic system can be involved in pain, both on the efferent and afferent side, even though only 10 to 20 per cent of C fibers are related to the sympa-

* From a symposium on Pain, presented at the Annual Meeting of The American Society of Anesthesiologists, Inc., December 9, 1949.

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thetic. Pain impulses can run up afferent fibers that are clearly in the autonomic system; stimulation of sympathetic ganglia can cause pain (4) and the autonomic can carry pain past a cord transection (5, 6). Vasomotor and other autonomic afferent fibers have been explored extensively, and such peripheral effects as dilation or constriction, excessive pulse pressure, liberation of H substance, tissue edema, and pressure of a scar on a nerve have been invoked in the genesis of causalgia. None of these is critical, however, and it is well to remember that compression blocks A fibers before C and cocaine blocks C before A, and that, although anoxia lowers the threshold of pain fibers and may give spontaneous firing, these are normally insensitive to pressure (2, 7, 8).

The phenomenon of cross talk, or artificial synapse, can occur between fibers that have become oversensitive to the electrical fields of their neighbors (9, 10). This breakdown of the law of isolated conduction so that sympathetic efferent impulses excite somatic afferents (11) does not, however, seem an adequate basis for causalgia. It does not account for the greater frequency with high lesions or stretch (12), nor for the persistence or recurrence after high nerve section or sympathectomy or even amputation, nor, for that matter, the rarity of causalgia after nerve trunk injury. Indeed, I would like to discard the whole problem of the periphery because, in my judgment, no matter how necessary it may be in the initiation of causalgic phenomena, it has become secondary and unimportant by the time one is dealing with a really developed causalgia. The most direct evidence of this is that, when such pain has persisted for a sufficient time, no peripheral operation relieves it. The disturbance somehow has moved into the central nervous system.

A second important phase of the problem that I shall merely allude to concerns the actual coming into consciousness of pain, whether in the thalamus or cortex or elsewhere. Considerable evidence, accumulated particularly in recent years, suggests that pain consciousness has more to do with the cortex than had usually been believed, even though not predominantly there. Pain has occurred with focal epilepsy and been abolished by local excision of a bit of cortex (13). Similarly, phantom limb pain has been relieved by cortical operation (14). Stimulation of the postcentral gyrus, in turn, has evoked pain awareness (15). It remains true for the most part, however, that cortical manipulation is not related to pain; indeed, bilateral pain seemed normal in a patient with an entire hemisphere missing (and corresponding thalamic degeneration) (4), as pain may be absent with a presumably normal cortex (16). Leukotomy, even unilateral leukotomy, seems able to relieve the "inconvenience" and unpleasant affect of pain, but this seems less the result of decreased sensation than of decreased attention to the sensation (17). Again, this cannot be the region that demands really critical analysis, since a double tractotomy eliminates the pain in all

but the most prolonged and delayed cases, in which the whole pathologic process has moved cephalad. Rather, some abnormal pattern of nerve impulses reaches the upper part of the nervous system, and just where is now unimportant, which gives rise in consciousness to this horrible type of suffering. We must focus, then, in our physiologic analysis, on some kind of maintained disturbance in the spinal cord.

Briefly, the outstanding phenomena of causalgic type pain are as follows. It is a slow, burning, poorly localized and irradiating pain, easily provoked by peripheral stimulation (at or above normal thresholds) or by central facilitation (especially by emotional states), with a peculiarly unpleasant quality and associated with such severe affective reactions that the personality may be strikingly altered. Particularly, it tends to increase in time and to spread in space. It has a devastating ability to leak around any kind of surgical block interposed in its path. The pain exhibits the tendency, seen in the course of evolution of the nervous system itself, of progressive centralization and cephalization of its site. Central pain is common only when pathologic change involves the grey matter proper (18). We have, then, this basic problem of a maintained, abnormal, dynamic state of the cord neurons. It is the nature and mechanism of production of this state to which attention is now directed.

First, what is the essential change? A view almost seventy years old (19), which has received reinforcement from observers at regular intervals since (20, 1), is that the fundamental abnormality is some sort of overactivity, perhaps an increased subliminal fringe, that the cells (21, 12, 1) develop. I have called this a "physiological inflammation" (22) of the neurons of the cord, some abnormal hyperactive state of the neurons associated with the bombardment of these neurons by excessive impulses. The evidence for an interpretation in terms of overactivity is convincing, even dramatic. The relevant findings can be summarized under the headings of reinforcement and of block.

First, the pain is exacerbated by a variety of peripheral or central stimuli. The existence of peripheral trigger points, able to provoke an agonizing bout of the pain, is well known. The gentlest stimulus of skin or muscle, even light in the eye (12; compare the augmentation of auditory impulses by visual activity, 23) may suffice. Recent laboratory work (24, 25, 26) has shown that trigger zones, associated with chronic skeletal or visceral lesions, often can be demonstrated objectively in terms of areas of lowered threshold or skin resistance, increased blood flow and the like. Injection of a fraction of a milliliter of irritant hypertonic salt solution into the spinous ligaments at the appropriate segmental level can bring about, in patients who had had a renal colic, cardiac angina or other visceral pain syndrome, a recrudescence of the typical pain picture in each case (27). The irritation, so to speak, created trigger points. Conversely, others report that injection of cocaine into a trigger zone in the pectoral region can relieve an

anginal attack (28, 29) or that injection of the interscapular skin can initiate crisis and resolution in lobar pneumonia (30).

Central reinforcement is probable in the increased pain with emotion, although in certain cases a peripheral factor, as increased muscle tension (31), may be involved. Menstrual pain, from uterine contractions, is enhanced by the increased muscle tone induced by apprehension (32), but purely central effects probably contribute. Certainly, the reaction to pain, even to a pain stimulus subthreshold to perception, is exaggerated by fear (31; not found in recent studies, 33). Central reinforcement and irradiation are, in fact, of very general occurrence. Even the spread of deep pain from one cooled finger to adjacent ones is entirely central, since it occurs when the nerves from the adjacent fingers are blocked (31).

The second main line of evidence, for some kind of overactivity owing to maintained overstimulation, is that early interruption of afferent impulses by transient nerve block often relieves the pain permanently. The clinical efficacy of single or repeated nerve block is too well accepted to require discussion, but some specific experiments deserve mention. On the basis of clues from other studies, referred pain to filled teeth was examined (34). Symmetrical cavities on the two sides of the mouth were filled, using equal technical skill, but, on one side, maximal care was exerted to protect the patients' sensibilities while, on the other, all analgesia was eschewed and the handling was a bit rough. In all of thirty odd cases the subject developed, in the roughly handled tooth, a severe referred pain from mechanical stimulation of the maxillary antrum. This never appeared on the control side. Such pain patterns remained indefinitely, unchanged over many months, with no further manipulation. A single procaine block of the roughly handled tooth, however, although worn off in a few hours, permanently abolished the referred pain. Here, then, is strong evidence that an initial excessive afferent barrage had set up in the central nervous system a modified functional state, continuously reinforced by a steady but not particularly excessive train of impulses from the periphery, and that temporary interruption of the peripheral reinforcement sufficed to allow this central abnormality to subside. After the inflammation had subsided, the normal flow of impulses neither reinforced nor reestablished it.

This evidence by a maintained overexcitatory state in the cord is easily supplemented by other types of experimentation. A source of irritation, a *locus resistantiae minoris*, was produced in patients with anginal pain by injecting a vesicant into the skin on the right chest (35). In time the irritation completely disappeared, leaving no local signs; nevertheless in subsequent anginal attacks the pain, previously limited to the left side, now regularly radiated in addition to this particular region on the right side. Even more dramatic evidence of an enduring central change was obtained by injecting turpentine into the

paw of a cat (36). This produced severe pain, limping, flexion and the other phenomena of attending a severe local irritation; in time the symptoms had completely vanished, the cat was running around entirely normally, and there was no reason to suspect that any residue remained. Nevertheless, when the animal was then decerebrated by an intercollicular section, the decerebrate rigidity that resulted was not symmetrical. The posture of the hind legs was exactly that seen in the flexion reflex produced by severe painful stimulation of the nerve from one leg; the previously injected leg was kept in strong flexion, the other in crossed extension. There is even a claim (37) of unilateral histologic changes in the cord of such an animal. Finally, placing aluminum cream in the motor cortex of a monkey, even if excised after four days, can lead to focal epilepsy three months later (38). Comparable injection of this agent into the lower cord of the cat has generated a spreading causalgia-like hyperalgesia well ahead of the initial point of injection (39). Some kind of maintained overactivity of central neurons is present and continuously reinforced, at least at first, by the arrival of impulses from the periphery.

Yet there exists another, equally impressive, body of evidence which points in exactly the reverse direction. This leads to an interpretation of causalgia, not as a result of overdriving but as a result of loss of impulses, as defective rather than excessive innervation. This general conception also has a long history, at least from the studies of Holmes on the dissociation of epicritic and protopathic sensation and the view that the former, perhaps by way of the cerebrum, holds in check diencephalic responses to the latter (20). That cortex can inhibit hypothalamus (40) and thalamus (41) is established, but reverse relations also exist (42) and, in any event, these cephalic relations are not disturbed in causalgia. A related suggestion (43), however, has been offered specifically to account for causalgia pain. A peripheral stimulus normally leads to two sets of ascending cord impulses; the fast, epicritic-like messages reach a thalamic relay in time to inhibit there the slow pain impulses, which are thus largely kept from the cerebrum and consciousness. This interesting view is at least partly right, for electrophysiologic work (44) has demonstrated such fast and slow ascending paths. Unfortunately, in these experiments the fast impulses condition the brain stem centers positively and enable the slow ones to pass upward more easily; but this need not be the action in all such systems, for inhibitory conditioning is also well known (e.g. 45). Considerable clinical experience is in harmony with such a view. In pruritus ani (46) for example, section of the anterolateral columns, in which travel the "protopathic" pain tracts, tends to relieve the symptoms, while a more dorsal section, destroying the touch-pressure fibers, far from relieving pain, exacerbates the whole pain syndrome.

Further evidence of interaction between sensory modalities comes from studies on peripheral nerves. A pressure cuff on the arm leads,

after about a half hour inflation, to a fairly abrupt loss of fast pain sensation from the lower arm and to loss of touch and temperature shortly before or after this (47). At that time the slow pain is suddenly exaggerated and acquires the peculiar burning, unpleasant, suffering-producing quality of causalgic pain. The obvious interpretation is that, when the larger fibers fail (and experimentally they do block first under pressure or asphyxia, 2), the small pain fiber impulses, no longer modulated in the cord, carry up and into consciousness the excessive and distorted awareness of pain. Perhaps the mere absence of other sensory modalities leads the cortex to overestimate those which do arrive (48). There are some difficulties with this interpretation, but they can be passed by since recent work makes even this dichotomy perhaps unnecessary.

Careful physiologic assay of sensations from a given skin area followed by excision and histologic mapping of nerve endings has yielded important information, especially following damage to the cutaneous nerve (49). A critical finding dealt with a reinnervated skin area, part of which showed normal pain sensation while another part exhibited typical causalgic pain. Only normal pain fibers were found in both regions and their terminal nets also appeared entirely normal. In the region with undisturbed pain sensation, however, several pain fibers were present with their interdigitated terminal nets, while in the causalgic area only a single fiber and terminal supplied the innervation of a given skin region. Causalgic pain, then, is here attributed to the activity of single pain units, unmodulated by other pain units normally excited by the same stimulus. Even the cuff experiments might be the result of block of some slow pain fibers rather than of the faster fibers; and, indeed, causalgic pain has been found in a skin area which possessed touch sensibility (50).

A case has been reported (51) which is almost diagrammatic of the view that causalgic pain results from the simple loss of normal innervation. Following injury, three nerves in the arm regenerated so as to innervate the same bit of skin. Sensation from that bit was normal. After procaine block of one of the nerve branches, pain sensations became more unpleasant; after block of two, pain became completely causalgic in type; after block of all, anesthesia was complete. Here, then, is an example of progressive whittling down of the pain innervation by physiologic means, with a parallel appearance of excessive and abnormal pain experience. Another illustrative case (52) is cited. A man who had had a limb amputated twenty-nine years earlier was operated on (for some irrelevant condition) under spinal block anesthesia. During the time that the nerves were blocked and afferent impulses were prevented from reaching the cord, and only during that time, he complained of terrific causalgic pain in the phantom limb. No such sensation had been experienced previously. (I am grateful to several anesthesiologists who have informed me of entirely comparable, and

previously inexplicable, experiences from their own practice. It has also been called to my attention, by Dr. H. Davis, that tinnitus may be greatly reduced when ordinary sounds are present.)

I present a final point on the greater incidence of causalgia with nerve injury that is violent or close to the central system than under other conditions of injury. Such peripheral injury is commonly associated with the actual degeneration of neurons. Sensory neurons degenerate more easily than motor, and some four times as many of the small neurons of the spinal ganglia are lost as of the large ones (53). There is even significant transneuronal degeneration in Clarke's column (54). Thus, in cases of high, violent nerve damage there is almost certainly a considerable component of actual anatomic degeneration in the cord, with especial loss of the neurons serving slow pain (12). This is just the situation for producing causalgic pain.

Here, then, are two sets of evidence, each extremely convincing, one tracing causalgia to an initial overactivity and the other to an underactivity. Fortunately, these are not irreconcilable in terms of physiologic mechanisms; they are, in fact, quite in harmony with reasonable interpretations. We must account for an abnormal state of spinal neurons, set up by a combination of excessive activity of some afferent neurons and deficient activity of others, a state which exhibits first centralization and then cephalization and one which tends to increment in time and spread in space. The disturbance is not uniquely related to any particular anatomically defined neurons, but is a pattern involving neuron groups and able to shift its locus and so the actual units implicated.

Such a situation is by no means unique to causalgic pain. If the affective sign is reversed from unpleasant to pleasant, we would have a good description of the neurologic and psychologic consequences of stimulation of the external genitalia. The phenomena of motion sickness, from labyrinthine stimulation, seem comparable. In all there are marked summation, irradiation, prepotency, a vague and prevasive quality with a nonetheless intense affect and great susceptibility to both reinforcement and suppression by peripheral or central activity. On the motor side, epilepsy comes strongly to mind as a related phenomenon, and many of the attributes of neurosis are strikingly similar. Indeed, such cases as the following, for a description of which I am indebted to Dr. H. Jasper, supply a wide bridge between epilepsy and overt neurosis. A man had his first epileptic attack on seeing an object taken from a dog. Attacks recurred only on renewal of such an experience; but, over years, the precipitating situation became more generalized, to seeing anything taken from anyone, until observing a check-girl receive a customer's coat led to a full-blown episode. Also, the regular habit-forming action of analgesic drugs, and the ability of a leukotomy to relieve, if not pain, at least the pain's mattering, and to eliminate narcotic withdrawal symptoms (17) are impressive (a decor-

ticate addicted dog can, however, die on abrupt withdrawal of drug, 33); but such considerations lead further into the unknown.

That a certain type of neuron activity may depend on continued presence of impulses in some impinging nerve fibers and absence of impulses in others is well known. Even the alpha rhythm of brain waves depends on the arrival of some thalamic impulses but is disrupted by others associated with vision. An even sharper example was encountered in a regular rhythm in the optic thalamus of the cat (55). This rhythm, like the human alpha, is abolished by bright illumination of the eyes; but it fades away in an hour or two in complete darkness, when the continuous gentle reinforcement supplied by diffuse illumination is withdrawn. The physiologic mechanisms now require attention.

There could be, of course, the sort of chemical and morphologic mnemonic traces in synapses, often assigned to one type of memory, which would lower thresholds of an internuncial pool and increase the subliminal fringe. Or interneurons could be captured by certain arcs, when these are driven more than competing ones (56). Doubtless such mechanisms could be elaborated to fit the phenomena, but they seem less promising than others. Reverberating circuits are more interesting, indeed they are currently being invoked to account for much of neural physiology. The possibility that one neuron activates a second, this a third, and so on until the last one reactivates the first, leading to a trapped impulse running around and around in neuron circles (57), is theoretically most attractive. It could explain the present phenomena: a single input starts some neuron chain reverberating; additional impulses coming in out of phase or in other positions would tend to disrupt, but continued impulses in the appropriate channels would tend to reinforce and maintain it. Such reverberating nets could constitute the maintained abnormal dynamic state of the cord neurons. There are difficulties that could be met by subsidiary assumptions, but it is well to remember that even the existence of circuits so functioning remains at present an hypothesis. To my knowledge, they have not been actually demonstrated.

I am inclined to still another view, suggested to me by experiments we performed in an entirely different connection. It does not necessitate any neuron circuit; it requires merely that groups of neurons (perhaps considerable masses of neurons) become locked together in their spontaneous rhythms. The electrical rhythm in neurons, including the brain waves or alpha rhythm in many if not all cases, is a true autochthonous beat. The rhythm becomes larger and more regular in a few neurons removed from the frog's brain and examined *in vitro*; the nerve cells continue to beat electrically just as the heart does (58). Unless large numbers of those neurons are locked in step together, are beating in synchrony, the whole mass of them would give no electrical record, for, being out of phase, their positive and negative changes would counteract each other to give a neutral background. But they

are locked together—they are synchronized, and in varying degrees of goodness. The mechanism of synchronization we think we understand (59, 60); it depends on electric currents that flow through the intercellular fluids between neurons, not on nerve impulses running from cell to cell.

One can demonstrate this in the case of large alga cells, *Nitella*, which show a similar electrical beat. When several of these are

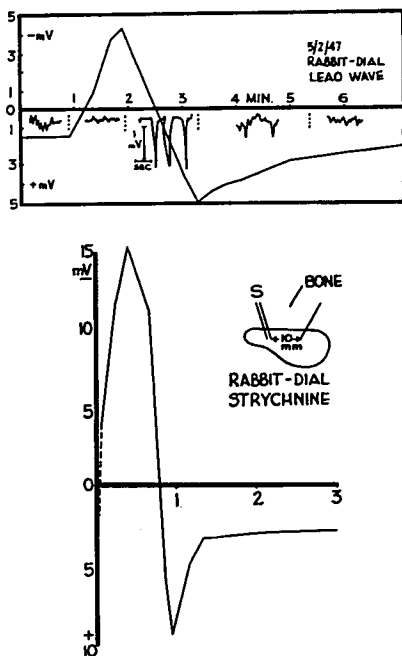


FIG. 1.

dumped on the bottom of a dish, not touching each other, at first each one beats at its own rhythm; soon a couple close together have somehow come into phase and are beating in synchrony. Their joint, and so more powerful, electrical field "captures" additional cells farther away, until finally all the cells in the dish are beating in unison. The more cells that beat together, the harder it is to break it up (61). Discharges from the cut end of a peripheral nerve similarly are at first independent in each fiber; after a while, especially if thresholds are low-

ered chemically, the fibers are firing together, and large waves of impulses ascend the nerve (62, 63). The same thing is true in the retina. The whole retina gives rhythmic beats with diffuse uniform illumination, whereas patterned illumination, which introduces extra impulses irregularly, breaks up the rhythm (64). The alpha rhythm of the human brain is comparably disrupted by light.

Evidence will not be developed here for the importance of steady potentials (D. C. fields), and currents in a volume conductor, for the functioning of neural masses. Such currents can give wave propagation across anatomic discontinuity, such potentials do exist and are considerable, and deliberately altering the potentials can start or stop neuron rhythms (65, 66). Figure 1 shows the striking D.C. potential changes in the mammalian brain associated with strychnine action and with the spread of cortical "suppression." (These records were first presented by my colleague, Dr. B. Libet, (67); they have not previously been published.) The more complete the interlocking of beating neurons, the more difficult it is to disrupt such hypersynchronization—by high potassium, for example, or by applied currents. The same is probably true for incoming out-of-phase impulses.

Thus, I suggest that in the cord, under causalgic conditions, a hypersynchronization, a firmer locking together of a larger than normal number of neurons, has occurred to form a pulsating pool, and that this synchronization has become exaggerated by virtue of the lack of disturbing impulses to disrupt the synchrony and by reinforcement with those specific pain afferents that are feeding in to lock the neurons (just as cortical neurons become locked in their beat by a flickering light). Such a pulsing pool could recruit additional units, could move along in the grey matter, could be maintained by impulses different from and feebler than those needed to initiate it, could discharge excessive and abnormally patterned volleys to the higher centers. In short, such a hypersynchronization could be the physiologic inflammation that would account for the phenomena discussed in this paper.

If this view is correct in principle, it would be worth seeking abnormal electric rhythms and perhaps D.C. potentials in the cords of patients who have causalgia—or of animals rendered causalgic (39). It would also be interesting to attempt to terminate causalgia by disrupting the neuron beat with applied currents, as electroshock is used on the brain. Whether or not such more remote possibilities work out, these physiologic considerations lead to obvious therapeutic suggestions. If the abnormality in the cord neurons is the result of excess activity in pain fibers and subnormal activity in other fibers, then the treatment should be to block the pain fibers combined with stimulation of the normal input. It is most impressive that physiology thus accurately predicts what clinical experience has found; nor is this "wishful explaining," for I was initially quite skeptical of the importance of a normal input. I agree with Dr. Livingston: block pain fibers as need

be, and then superimpose stimuli of the normal afferent systems. Cord depressants, which would tend to unlock the cells, might be therapeutically advantageous, but high potassium would affect the heart too early. Electrotherapy should be explored with caution.

Finally, our knowledge of the nervous system has advanced enormously in the last half century, and the picture of its activity has changed dramatically from that of a static telephone system to that of a far more complex, flexible, mobile, dynamic instrument (22). This change has come about in good part because neurophysiologists have had to consider new phenomena, discovered in many cases in the clinic and by clinical workers, which demanded scientific analysis and interpretation. Such phenomena force the experimentalist and the scientific theoretician into broader and more useful and certainly truer views of the real mechanisms of the nervous system. The clinician who observes carefully and allows himself to think about the meaning of his observations will do a great service to medical science by supplying the experimentalist with valuable stimuli. This is nowhere better illustrated than by the clinical contributions in the field of pain.

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