Reports

Evidence for a Double Peripheral Pathway for Pain

In a recent note (*1*) Jones reached the conclusion, after certain experimental procedures for pain stimulation, that "the best evidence of all varieties points to double pain as an artifact." She also indicated that she equates C-fiber pain with the second pain she could not demonstrate: "it seems difficult to believe that if there is a second, slower pain system leading to sensation, it would not appear. . . ." Since the author apparently misinterpreted our results (*2*) and also failed to note the significant point of the technique we employed, we take this occasion to amend her report.

When a peripheral skin nerve is stimulated electrically either percutaneously or with an inserted electrode, the threshold response perceived is one of a tapping touch sensation projected in the distribution of the nerve stimulated. This sensation remains unchanged regardless of frequency of stimulation until the intensity is increased 3 to 5 times. At this point a pricking pain sensation is produced by each shock, and the repetitive nature of the stimulus is perceptible at rates up to 30 per second (*3*). Comparable experiments in animals where the nerve action potentials were recorded, and some experiments in man where the nerve was removed for action potential recording, have shown that the pain sensation correlates with the delta spike of the nerve action potential. Collins (*4*) has confirmed these findings by recording the nerve action potentials *in situ* in man. Moreover, differential procaine anesthesia blocks pain and the small myelinated fibers, sparing touch and the large fibers (*5*). Thus fast pain is conducted by the small myelinated (delta) fibers of the A group.

When the limb is compressed by a blood pressure cuff inflated to a pressure of 250 mm-Hg for 35 to 45 minutes, *all* touch and pricking pain resulting from the stimulation of the distal skin surface is abolished. A deep aching pain which is delayed and exaggerated compared with the normal extremity can still be elicited by strong electrical stimulation of skin or by firm pressure; delayed warmth and cold may also be produced by appropriate stimuli. Electrical stimulation of a nerve trunk peripheral to the block, at a strength far above that previously required to induce touch and pricking pain, causes an obviously delayed excruciating burning pain which fuses and summates at a rate of three to five per second. This sensation is quite different in character from any sensation resulting from stimulation in the normal skin or nerve at weaker strengths before block. It is similar to the sensation derived from electrically or mechanically stimulated periosteum, as in a bruised shin. Where such pain is due to inflammation, it can be differentially blocked by procaine when pricking (delta) pain is intact (*2*). Correlated experiments in animals where the nerve action potentials were recorded have shown the behavioral response of pain when all but C-fiber afferents were blocked by pressure or electrical tetani (*6*). Thus slow pain is conducted by unmyelinated C-fibers.

Two volleys of subjective pain from single-shock electrical stimulation of an unblocked peripheral nerve have not been reported. The strength of electrical shock necessary to activate C fibers is many fold supramaximal for the delta fibers in the nerve and produces repetitive action potential responses. Such intense stimulation has made introspective observations impossible for us. In any case Jones did not stimulate peripheral nerves, and it is not certain what she stimulated in the skin when she did not obtain double pain from electrical stimulation.

We too reported that a biphasic subjective response to transient pain stimuli is often absent in normal subjects without nerve block. Our experiments with block show that two pain pathways exist, however seldom both can be identified introspectively when activated simultaneously under normal conditions. Each of these pains can be induced separately; they are qualitatively different and have quantitatively different latencies.

Jones' statement that we obtained "somewhat similar results" (to hers) following immediately the categorical statement, "Double pain was not found with normal subjects under controlled conditions," seems to indict either our experiments or our normality, besides being incorrect. As to her further statement that "the argument that a second pain system is suppressed by the faster system lacks evidence," we can only invite her to repeat the experiment with block and thus differentiate between argument and experiment.

We have previously pointed out (*2*) that the assignment of sensory experience to the results of stimulation of particular nerve fibers in experiments with a differential block are valid when an absolute end point of the absence of one experience or another is used. Arbitrary end points (*7*) must correlate with incomplete block of populations of nerve fibers; thus the conditions of experiment necessarily obscure the correlation of loss of sensation with loss of a fiber group, since the sensory end point by definition occurs before all the nerve fibers in any group in question are blocked. The fact that anatomical techniques have been inadequate to disclose structural differences in nerve endings which correlate with modalities of sensation cannot disprove the physiological observations related to nerve fiber diameters, thresholds, and conduction rates.

Recently Douglas and Ritchie (*8*) have shown that, in the cat, tactile stimulation produces afferent impulses in a faster subgroup of C fibers. If species differences are excluded from consideration, then the fact that no tactile sensation persists after block of myelinated fibers in man must indicate either that fast C fibers are blocked along with delta fibers or that *the perception of pain requires activation of a critical amount of C-fiber afferent activity*. In our experiments the cat saphenous C potential has been unchanged after compression block of A fibers; it would obviously be useful to know how pressure block affects Douglas and Ritchie's preparation.

While dealing with the functions of C fibers, we wish to add a statement that one of us was incorrect in implying that itch is a specific sequel to weak stimulation of delta fibers (*9*). Concurring with others (*10*) who have reported that C fibers are partly or entirely responsible for itch, we have found that the action of cowhage (itch powder) at the wrist persists after tourniquet block (35 to 40

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper. (Since this requirement has only recently gone into effect, not all reports that are now being published as yet observe it.)

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to Contributors" [*Science* 125, 16 (1957)].

minutes) of all touch and pricking pain. It was noted that itch can be relieved by scratching even when the scratching itself cannot be felt. In one tabetic patient who lacks pricking pain and has exaggerated delayed pain, cowhage produced itch also. Using Shelley and Arthur's technique of implanting a small stimulating wire in the subepithelial layer of the skin, we find in the normal state a pricking itch, which becomes a most exquisite slowly summating "natural" itch after the block of large myelinated fibers. Shock intensity necessary to elicit itch increases up to several fold during pressure block.

Whether the itch of subepithelial C-fiber stimulation and the burning pain produced by C-fiber stimulation in nerve trunks relate to different numbers, groups, or patterns of pain fibers, or to different methods of stimulation is not determined. It still seems probable that a component of itch sensation is mediated by delta fibers as previously inferred.

In summary, we believe that it has been demonstrated that a second, long-latency pain is obtained after block of short-latency delta fiber pain. A similar sensation follows any painful stimulus in patients with tabes dorsalis who lack pricking pain, and the "protopathic pain" in the margin of denervated areas is of the same type. Differential blocks in these conditions, along with our own pressure block experiments, indicate that pain from C-fiber stimulation is enhanced by the absence of the myelinated delta pathway. We conclude that the failure of ourselves and others consistently to demonstrate two pains from one stimulus to the skin surface is due to the inadequacy of this experimental procedure as a differential method (*11*).

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References and Notes

1. M. H. Jones, *Science* 124, 442 (1956).
2. W. Landau and G. H. Bishop, *A.M.A. Arch. Neurol. Psychiat.* 69, 490 (1953).
3. P. Heinbecker, G. H. Bishop, J. O'Leary, *ibid.* 29, 771 (1933).
4. W. F. Collins, personal communication.
5. P. Heinbecker, G. H. Bishop, J. O'Leary, *A.M.A. Arch. Neurol. Psychiat.* 31, 34 (1934).
6. D. Clark, J. Hughes, H. S. Gasser, *Am. J. Physiol.* 114, 69 (1935); G. H. Bishop and P. Heinbecker, *ibid.* 114, 179 (1935).
7. D. C. Sinclair, *Brain* 78, 584 (1955).
8. W. W. Douglas and J. M. Ritchie, *J. Physiol. (London)* 139, 385 (1957).
9. G. H. Bishop, *J. Neurophysiol.* 6, 361 (1943).
10. R. G. Bickford, *Clin. Sci.* 3, 377 (1938); D. T. Graham, H. Goodell, H. G. Wolff, *J. Clin. Invest.* 30, 37 (1951); W. B. Shelley and R. P. Arthur, *A.M.A. Arch. Dermat.* 76, 296 (1957).
11. This work was supported in part by the Office of Naval Research [contract 816 (03)] and by the U.S. Public Health Service (grant B-882).

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Bishop and Landau obfuscate the several issues involved. The primary issue, and the one toward which my experimental investigation (*1*) was directed, is whether double pain sensations (awareness) from a single stimulus can be observed by a normal subject (the intact organism—neither tabetics nor amputees nor individuals with regenerating nerves, ischemic limbs, or nerve blocks) under properly controlled conditions of stimulation of cutaneous receptors, and at some psychophysically identifiable level of intensity. The reasons for concern with this issue are (i) descriptions of "double pain" as a normal sensory phenomenon are often encountered (*2*) and (ii) "double pain" is sometimes used as a measure of the effectiveness of a drug (*3*). In the first case, it is important for the scientific description and measurement of normal (nonpathological) sensation that the issue be clarified. In the second case, it is important in the evaluation of drugs that artifacts not be used as criteria of effectiveness.

The evidence points to double pain as an artifact of method when the normal organism (as defined above) is involved. Landau and Bishop, in spite of their present apparent disclaimer, did originally report (*4*) "somewhat similar results"—their experiment on eight normal, "unprejudiced" subjects, with heat, electrical, and brief mechanical stimuli showed that only three "thought" they could recognize a second pain response. I do not indict their experiment, for we are given no information on which to do so. But I do indict their inadequate report of it, and also the implication that their subjects were given the suggestion that there might be a second pain. Their present statement that "a biphasic subjective response to transient pain stimuli is often absent in normal subjects . . ." is the point I wished to emphasize. Without further information about stimulus control, instructions to the subject, or method, I cannot be sure whether the three subjects who "thought they could recognize" a second pain response were genuine positive cases or not. Since all the cases I have discovered—in normal subjects—can readily be explained by double stimulation, temporally or spatially, I must assume, evidence to the contrary lacking, that these can be so explained also. It is certain that hand-held needles and hot objects are totally unsuitable as stimuli for the investigation of this phenomenon. I am still of the opinion that the best evidence indicates that double pain as a normal sensory phenomenon is an artifact of method, for the reasons I originally set forth.

The second question, of the existence of a second pain system, demonstrable under abnormal physiological conditions, is quite distinct from the first and is inherently much more complex. Two of the basic issues are the following. (i) What are the facts and what are the assumptions. (ii) How far can one trust data obtained from pathologically functioning tissues in interpreting normal function.

The arguments for the existence of a second pain system stem most importantly from the various nerve-block and ischemia experiments [since the reaction-time evidence must be rejected as uncontrolled (*5*)]. I have already indicated (*5*) that I believe the nerve-block-ischemia data to be based upon pathological tissue conditions, and as such they must be interpreted with caution.

It is not easy to separate the facts from hypotheses or from experimental errors. I am willing to assume the following as facts:

1) After inflation of a sphygmomanometer cuff on a limb (which is partly pressure-block and partly ischemia, the balance of these and the nerve fibers affected varying with location and care in cuff application), reliable reports are obtained from human subjects that, after a period of time (variable), the sensory quality of pain evoked by noxious stimuli applied to receptors changes from a well-localized 'pricking' pain to a diffuse, burning or aching pain with greatly increased affect, even without intensity (subjective) change.

1A) Under the same conditions, the human subject reports a considerable delay in perception time.

2) In recording of nerve potentials from animal preparations, noxious stimuli evoke action potentials in small unmyelinated fibers called C-fibers.

2A) In the same situation, compression block of the nerve results in progressive disappearance of action potentials, in general the larger, myelinated fibers succumbing first, the small unmyelinated fibers surviving longer.

The connection between these two sets of data is hypothetical and is based on a number of assumptions, as well as on approximate temporal coincidence.

Qualitative argument. The assumption is that, since pain changes in quality after interference with normal physiological functioning, a new set of fibers is required. It is clear that touch, warmth, and cold also show similar qualitative changes (*6–8*). Furthermore, in other situations in which pain is poorly localized (as in visceral pain) and where the number of fibers subserving an area is reduced (as in partially denervated areas), a similar diffuse, burning or aching pain is present. I would assume the qualitative change to be due to a change in the temporospatial afferent pattern, following a reduction in number of active fibers, since there will, of course, be a distribution of survival times for the total population of the neurons in question.

Delay argument. The assumption is that, since perception of pain is delayed, a different set of neurons, with slower conduction times, is required. There is good evidence for a progressively increasing latency of action potentials in blocked nerves. Clark, Hughes, and Gasser (*9*) found slight slowing of conduction rates apparent within 15 minutes. Records of action potentials in the human ulnar nerve show progressive increase in latency after inflation of the pressure cuff (*10*). There was no discontinuity in the curve as would be expected if the composition of the group of active neurons had changed. Similar delays in perception occur in the other cutaneous senses also (*6, 7*). I would assume the perceptual delay to be due to the increasing latency of action potentials in neurons subjected to pathological conditions, and possibly also to synaptic delays occasioned by reduction in number of afferent impulses reaching the central nervous system.

Reliability of ischemia-nerve block data. The assumption is that such data are reliable and give reliable indices of conduction times of fibers. It is clear that the results of such experiments on human subjects are variable. If a large number of subjects is used and if the results are treated statistically (*6, 7*), the order of loss is seldom significant. Landau and Bishop themselves (*4*) found procaine blocks to be "inconclusive" because prick and deep pain disappeared together—that is, because the sensory results did not bear out the results of action-potential studies. Whereas touch may usually fail before pain in compression of a limb, the difference is not sufficiently dramatic to enable one to distinguish between small delta fibers and C fibers. There is evidence that the survival time of fibers under compression block is influenced by factors other than conduction rates. Frankenhauser (*11*), who dealt with touch fibers of different types, found that slowly adapting touch receptors in the rabbit were blocked later than hair touch fibers in spite of the fact that their conduction rates completely overlap those of the latter. He concluded that the fibers themselves have properties which are not predictable from observation of the impulses. In man, skin touch and hair touch also have different survival times (*12*), and in some areas hair touch survives pain (*6*).

There are some interesting results which suggest that the somatic sensory apparatus is much more complex than the current popular notions would have it. Between giving up all specificity, as Sinclair (*13*) does, and being bound to one or even two specific pain modalities, as Bishop and Landau are, one can conceive a rich patterning of general somatic sensation, with a large number of different sorts of receptors having different functions and different response characteristics. Maruhashi, Mizuguchi, and Tasaki (*14*) found a great variety of types of afferent nerve fibers in the toad and cat. These varied not only in fiber size, but in type of discharge (tonic or phasic), size of receptive field, and type of stimulus most effective. I would assume that a given stimulus excites more than one kind of fiber; thus the perceptual pattern is normally a complex one, not only spatially and temporally, but also in the balance of fiber types activated. And a different stimulus, since it affects a dynamic organism, will have a different effect.

My conclusions are as follows. (i) The exact function of the C-fibers is not known. These fibers respond to noxious stimuli but whether this results in awareness or merely feeds into either the reticular activating system or into an "affect" system is not certain. (ii) The peculiar quality and delay of pain sensations in nerve-block experiments are probably due to pathologically functioning tissues. (iii) Somatic sensation is a vastly complex system. (iv) Second pain is certainly an artifact in normal human experience.

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References and Notes

1. M. H. Jones, *Science* **124**, 442 (1956).
2. For example: J. F. Fulton, Ed., *A Textbook of Physiology* (Saunders, Philadelphia, ed. 17, 1955), p. 335.
3. For example: R. R. Sonnerschein, *Proc. Soc. Exptl. Biol. Med.* **83**, 831 (1953).
4. W. Landau and G. H. Bishop, *A.M.A. Arch. Neurol. Psychiat.* **69**, 490 (1953).
5. M. H. Jones, *Science* **126**, 258 (1957).
6. D. C. Sinclair and J. R. Hinshaw, *Brain* 73, 224 (1950).
7. ———, *ibid.* 73, 480 (1950); 74, 318 (1951).
8. G. Weddell, D. C. Sinclair, W. H. Feindel, *J. Neurophysiol.* **11**, 99 (1948).
9. D. Clark, J. Hughes, H. S. Gasser, *Am. J. Physiol.* **114**, 69 (1935).
10. J. W. Magladery, D. B. McDougal, Jr., J. Stoll, *Bull. Johns Hopkins Hosp.* **86**, 291 (1950).
11. B. Fraukenhaueser, *Acta Physiol. Scand.* **18**, 75 (1949).
12. D. C. Sinclair, *J. Neurophysiol.* **11**, 75 (1948).
13. ———, *Brain* **78**, 584 (1955).
14. J. Maruhashi, K. Mizuguchi, I. Tasaki, *J. Physiol. (London)* **117**, 129 (1952).

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Tolerance to Cereal Leaf Rusts

Resistance of crop varieties to plant rust fungi has been attained thus far mainly through utilization of the hypersensitive reaction wherein the host and parasite are mutually incompatible, resulting in localized necrosis of host tissue and in death or limited growth of the parasite. Such hypersensitivity, hereafter referred to as resistance, has afforded excellent initial rust protection to new resistant varieties produced by plant breeders. However, when such resistant cereal varieties have been extensively grown, new virulent varients (physiologic races) of the rust fungi have consistantly arisen to render these varieties fully susceptible in nature. Three genetically distinct hypersensitive types of resistance to the crown-rust fungus, *Puccinia coronata* Cda., have been transferred to extensively grown, commercial oat varieties in the United States. All such varieties, although providing high resistance to the initially occurring populations of the pathogen, have succumbed to attack by new physiologic races within a few years after they have been extensively grown. A similar fate has befallen oat and wheat varieties once resistant to prevalent races of stem rust, *Puccinia graminis* Pers. These experiences direct attention to the need for plant characters, other than resistance, whereby rust damage may be prevented or reduced.

Tolerance, enabling a susceptible plant to endure severe attack by a rust fungus without sustaining severe losses in yield or quality, is such a character. Caldwell *et al.* (*1*) have shown that the yield of Fulhard wheat in Indiana is not affected by severe attack of the leaf-rust fungus, *Puccinia recondita* Rob. ex. Desm. f. sp. *tritici.* This finding was supported by the report of Salmon and Laude (*2*) that the Fulhard variety was the highest yielding of 24 varieties studied over a period of years in Kansas, although it was one of the most severely attacked by leaf rust.

Evidence that a high level of tolerance to the crown-rust fungus, *P. coronata,* exists in the Benton variety of oats was obtained in studies at Lafayette, Indiana, from 1955 to 1957. Two pairs of oat varieties were involved in these studies, each pair being nearly "isogenic" except that one member of each pair was highly resistant to crown rust while the other was highly susceptible. Pair No. 1 consisted of the varieties Clinton 59 and Clintland. They differed essentially by a genetic factor for resistance to crown rust which had been introduced into Clintland by a cross of Clinton 59 × Landhafer, followed by three backcrosses to Clinton 59. Pair No. 2 consisted of the varieties Benton and Bentland that also differed mainly by the same genetic factor for resistance which had been introduced into Bentland by a cross of Benton × Landhafer, followed by six backcrosses to Benton.

There is little difference between the members of these pairs of varieties in appearance or in yield and quality of grain, when grown in the absence of crown rust, as was shown by 16 replicated field-plot trials conducted in Indiana from 1954 to 1956 by Newman *et al.* (*3*). Crown rust was absent in 15 of these trials and occurred as only a trace in one. The mean yields and bushel weights of the two pairs of varieties for this period, obtained under crown-rust-