RECENT ADVANCES IN THE NEUROPHYSIOLOGY OF PAIN * † ‡

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THERE are few fields of research where concepts are undergoing more notable change than in neurophysiology. This has been brought about largely through the development of precise techniques of stimulation and recording within the nervous system, and an increasing attention to the multi neuronal pathways. Implant electrodes have made possible the study of subjects in their normal waking state, and have helped focus interest on the mind-brain relationships which for so many years have been considered outside the field of physiology. We now hear much about the reticular formation and its role in arousal—an area that was largely silent in the anesthetized brain of the standard laboratory preparation in the past. These developments are of great significance to the anesthesiologist, because further study of the anesthetized brain compared to the unanesthetized may well bring a better understanding of the way in which anesthetics act. Such developments are also of great importance to a better understanding of problems in pain.

The anesthesiologist who treats patients with pain problems will find a certain number in whom he is unable to bring about any significant measure of relief. Patients who later undergo rhizotomy or chordotomy may also fail to obtain lasting relief for the perception of pain may be replaced by vague, disagreeable feelings that are more troublesome than the pain itself. We then begin to speak of "central pain," and consider that the disturbance of sensation has moved "upstairs." We have generally accepted the concept of the vicious circle which can maintain itself at cord level even though the original site of stimulation no longer exists. Many now consider that the same mechanism can be maintained within the brain stem. Attempts have been made to interrupt the pain pathways in the mesencephalon, but such attempts have not been too successful. It becomes increasingly evident that our knowledge of the way pain reaches consciousness is very elementary.

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Most of us have been taught that pain is a specific sensation in the same way that sight, smell and hearing are specific. A short review of the pain pathways as we have learned them is in order if we are to understand wherein changes in concepts are occurring.

PATHWAYS AND THE PERCEPTION OF PAIN

The peripheral receiving apparatus for pain is generally considered to be the simple free endings whose arborizations may extend over as much as a square centimeter. Other specialized endings are considered to be specific for heat, cold, and touch, and no matter what the stimulus, the end organ is supposed to report its modality only. It is commonly assumed that the free endings are branches of the C fiber, and that this group of non-myelinated fibers are the transmitters of pain. Recent textbooks distinguish between "fast" and "slow" pain, and ascribe the transmission of "fast" pain to the smaller fibers of the A group. As these fibers branch terminally, they may lose their myelin sheaths and contribute to the network of free nerve endings that make up the unit for pain transmission. The cell bodies of the primary neurons lie in the dorsal root ganglia, and send fibers into the spinal cord where they bifurcate into ascending and descending branches. These terminate on secondary cells in the substantia gelatinosa. The secondary neuron may form simple reflex arcs with motor neurons, or may synapse with neurons within the internuncial pool; or it may cross over in the ventral commissure to the surface of the cord on the opposite side, to form the lateral spinothalamic tract. These fibers now pass up the cord through the brain stem to synapse with neurons of the third order in the thalamus. From here the pain message is carried to the sensory cortex.

This is obviously a simplified explanation but it is sufficient for the present purpose. With this outline of the pain pathways as a basis, some investigators believe that the amount of pain felt by an individual can be gauged according to the intensity of the peripheral stimulus. They believe that the threshold at which pain is first felt is highly predictable and that intensity of pain can be judged in steps from threshold pain to a maximum, quite apart from its associated meaning to the individual. The theory holds that "perception" of pain and "reaction" to it are separate entities.

Our group doubts that there is such a thing as a pure sensation of pain separate and distinct from the influence of reaction. We believe that there are so many neuronal influences modifying the input from a pain source before it reaches "awareness" that what we feel as pain is entirely dependent upon the momentary status of the central nervous system at the particular time the stimulus occurs. Some of the recent neurophysiological developments that cast doubt on the older concepts are the following.

CONCEPTS REGARDING THE SENSATION OF PAIN

Starting at the periphery, there is new evidence that the endings are not as specific for modalities (heat, cold, pain, touch) as we have formerly believed. In fact, the concept of modalities is held by some neurophysiologists to be a manner of speaking rather than an actuality. No one denies that there must be some specificity within the afferent system; but not as Von Frey postulated, with a specialized receptor for each modality. The skin of the human ear, for example, has but two morphologically separable endings, free fine terminals and basket-like networks around hair follicles—yet heat, cold, pain, and touch are felt there as well as in areas where the organized endings are seen (1). Tasaki (2) has reported on the kind of stimuli needed to cause impulses in single, unmyelinated, afferent fibers in the cat. He concluded that a mechanical or noxious stimulus to the skin set up impulses in more than one type of fiber, and was unable to correlate the fiber with a particular end-organ. He further postulates that our "pain" and "pressure" sensation is aroused by the concurrent activity of several different kinds of sensory units. It seems wise to modify the concept that pain has its own neural apparatus, as distinct in its way as is the sense of sight or hearing, and to look further for an explanation of how pain is felt.

We are far from the solution at this time. However, our pain study group has agreed upon certain points that may indicate the way investigation should take if the answer is to be supplied. First, we believe that the essential part of pain is *awareness*, and we are unwilling to call anything pain unless it is felt as such. The patient under a general anesthetic, then, has no pain during surgery, even though the peripheral apparatus is transmitting impulses along the primary pathways to the cortex. Boxers who are being severely beaten in the ring have reported that they feel no pain during the fight, yet their sensory apparatus is intact and carrying its messages centrally. Past experience, suggestion, and emotional states can all alter our awareness of pain, and in all likelihood many other factors, including those generally called "reaction" to pain, will alter the final pattern of what we feel.

Another development of importance has been the work of Magoun (3) and his co-workers on the ascending reticular system. Little was known of the functions of the nerve cells that lie in the brain stem, interspersed between the fibers of the main sensory and motor pathways, until Magoun showed that the area had something to do with arousal from sleep. If the reticular formation is stimulated while an animal shows a sleep pattern on the electrocardiogram, the pattern will change to the dys-synchrony of the waking state. If this area is destroyed, the animal remains in a persistent somnolent state and strong sensory stimuli only arouse him briefly. On the other hand, if the

main sensory pathways are destroyed at the upper level of the brain stem, peripheral stimuli will still waken the sleeping animal with an intact reticular formation. This indicates that the main sensory pathways send collaterals into the reticular formation, and the hypothesis is warranted that these collaterals have as much to do with the perception of pain as do the main pathways to the cortex, if not more so. Further work by the same group of investigators shows that the activity of the reticular formation is greatly affected by the anesthetic agents, and we have found in our laboratory that even analgesic concentrations of nitrous oxide exert a definite effect on transmission within this secondary sensory pathway. While our understanding of the functions of the reticular formation is still in its earliest phases, the existence of a polysynaptic pathway in the brain stem that corresponds in many ways to the internuncial pool at cord level has led our group to view the organization of the nervous system as a vertical or longitudinal system rather than one that has horizontal stratification, with the cortex at the top, and the spinal cord at the bottom (4).

NEWER ANATOMIC CONSIDERATIONS

It has been our teaching in comparative anatomy that the central nervous system has developed through a slow process of evolution, with each addition dominant over the one next in the phylogenetic scale. The cortex is considered the thinking part, with its highest development in man as evidence. We have so compartmentalized the spinal cord, for example, that if referred pain does not fit into the pattern of dermatomes, we may doubt its reality. Our pain study group prefers to consider the nervous system as having *three* main divisions dispersed in longitudinal manner from cauda equina to the cortex. The main sensory pathways form one column, the motor pathways another, and an area between, which we call the "transactional component," forms the third. In it, we include the internuncial pool, the reticular formation, and probably the association areas. Collaterals pass into this "neuropil" from the main sensory and motor pathways all along the course from the cord to the cortex and from cortex to cord. It has been demonstrated that the sensory input feeding into the neuronal pool acquires temporal and spatial dispersion. It has also been shown that the motor outflow may be markedly affected by the activity of these same neurons, not only those in the internuncial pool, but the neurons in the brain stem reticular formations as well. Sensory input can be experimentally dampened down by stimulation of the reticular formation, and there is no reason to believe this does not happen normally as well. What we feel as pain, then, is dependent upon the final pattern of impulses that reaches "awareness," and this is subject to modification at all levels from the point of entry to the sensorium.

We consider that moving from the rigidity of concepts embodied in the doctrine of levels and specificity to a more realistic, flexible consideration of the function of the central nervous system will hasten the time when many problems in pain will have a solution.

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