Emerging Methods for Studying Neural Mechanisms in Man

THE investigator relies heavily on controlled animal experimentation, but ultimately he must turn to man himself as the subject for final corroboration of his hypotheses. The problem of species-variable responses makes this imperative, whenever feasible. Unhappily, human investigation while solving this problem raises others pertaining not only to methodology but to ethics and morality as well. It follows that studies in man which observe the "rules of the game" challenge the ingenuity and integrity of the researcher to the utmost. Yet the recent splendid work of Price and his co-workers in the study of anesthetic effects on the circulation show that it can and must be done in man if truly meaningful information is to be obtained. There are other examples. A similar approach to gain data on central nervous system processes is needed and it would appear that the time is at hand.

Acknowledging the brilliant advances made by neurophysiologists during the past half century in the assault on the unknowns of this most complex system, it is nevertheless obvious that the major share of this work has been done on animals, notably the cat, monkey and rabbit. Since these animals lay no claim to communication of their feelings (or thoughts) with man, we are left with an important gap in our knowledge which we must bridge by studies on man himself. Indirect approaches involving Pavlovian techniques in animals can never give final answers to subjective problems such as the nature of pain, its mode of transmission and interpretation, to cite one example of considerable interest to the anesthesiologist.

Until relatively recently, the instrumentation to study this field properly in man was not available. Notwithstanding its well-known propensity for "bugs," electronics is now providing the means to receive, transmit, amplify, record, sort, analyze and even, in a limited sense, to interpret the myriad of microelectric signals which make up the detectable manifestations of the functioning nervous system. It remains for us to exploit this technical potential by asking meaningful experimental questions of our subjects, at the same time respecting their right to a minimum of exposure to discomfort or danger.

In their paper in this issue of the JOURNAL, Abrahamian, Allison, Goff and Rosner give us a taste of exciting work being pursued in their laboratory at Yale, which exemplifies this new approach to the study of the effects of general anesthetics upon neural mechanisms in man. Using volunteers, they have applied a method devised by Dawson[1] in 1954 for studying cortical evoked responses which is at once safe and relatively simple in its performance, although the underlying principles can hardly be thus described. Briefly, they stimulate the median nerve percutaneously with a painless electrical signal and observe its central effect by means of the electroencephalograph (EEG) first in the unmedicated state and then during light thiopental narcosis. To sort out the small evoked potentials from the spontaneous activity of the usual EEG requires the help of sophisticated communication theory plus computer-averaging techniques, an approach originally applied in this field by Mary Brazier and her co-workers[2] at Harvard and at Massachusetts Institute of Technology about 1952.

The method promises to give information beyond that currently available from standard EEG interpretation. The authors believe that the late portions of the evoked response—which they classify as components 3, 4 and 5, and which are very susceptible to the depressant effects of premedication and thiopental—represent the cortical input from the "nonspecific extralemniscal" somatic sensory pathways whose importance in alertness and whose relation to the general anesthetic state were classically described by Magoun and his co-workers[3] ten years ago. If the assumption is true, we are now possessed of a tool for studying the ascending diffuse projection system which, until now, has been done only in animals with electrodes placed in the mesencephalon and diencephalon, a procedure hardly justifiable in intact man. Apropos of this, there have been studies in man with deeply placed electrodes, but these have been confined to the cerebral hemispheres of psychotic or epileptic patients during neurosurgical therapy.[4, 5, 6]

There seems to be corroborative evidence in direct cortical studies in man [7, 8] to relate components 1 and 2 of the authors' evoked response to input of the "specific lemniscal" paths to the cortex, but they admit in a previous publication [9] that there is less support for the deduction that components 3, 4 and 5 are produced by extralemniscal pathways. Indeed, studies of the surgically-isolated cat cerebral cortex [10] (a situation not likely to be investigated in man, except fortuitously) indicate that all the components of directly evoked cortical potentials, including the late waves of long duration, can be elicited without connections from below. Whether these differently evoked responses are strictly comparable is, of course, questionable. But the doubt is raised and, for the present, the interpretation of these data must be considered controversial.

Meanwhile, recent important studies by Collins and his co-workers at Western Reserve [11] on conscious man utilizing graded electrical stimuli to isolated sural nerve have clearly related pain to small fiber conduction in the A delta and C range (Erlanger and Gasser's classification), a finding which for years had been predicted from animal studies but which awaited confirmation in man.

These combined techniques, limitations though they still may have, give promise of providing us with a means of applying a quantitatively and qualitatively known stimulus to a peripheral nerve, hopefully percutaneously, with information forthcoming on at least a portion of its transmission through subcortical relays, both direct and indirect, on its ultimate arrival at the cerebral cortex, all while the patient describes his sensations. With this control situation, one can then proceed to study the effects of depressant and stimulant drugs in the same subject.

As a final thought, one wonders if it is beyond the "know-how" of present day electrical engineering to devise some sort of energy beam of essentially zero mass which could be directed to desired depths of the brain, there to serve as a locus for either stimulating or for recording from subcortical centers while inflicting insignificant tissue damage. The possibilities for study of the brain with such an instrument are intriguing.

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