rabbits, no significant change occurs in tension. Similarly, if estrogen and progesterone treatments are combined, the maximum tension of the uterus will not be significantly different from that in animals which were treated with estrogen only. This observation is in agreement with previous findings that progesterone domination does not significantly alter the actomyosin concentration (*10*).

Fig. 1 indicates the course of gradual increase in maximum tension as a result of the administration of estrogen. The curve is S-shaped. The increase in actomyosin concentration is also slight during the first few days of estrogen treatment (observations on this point were carried out only up to 4 days of estrogen treatment).

These observations indicate that the maximum isometric tension developed by the uterus depends in a final sense on the concentration of actomyosin, and thus the term "contractile protein" seems to be adequate.

In conclusion, we wish to emphasize the singular behavior of uterine muscle with respect to estrogen, which is characteristic, so far as known, of no other muscle. The final contractile system being dependent upon this specific hormone, we are able to make it disappear and reappear again in a fully grown animal as many times as the experiments require. Changes in actomyosin concentration in skeletal muscle related to hormone levels or other physiological conditions have not as yet been observed, except during the process of embryonic development, and no means is known of causing regeneration of the final contractile system in skeletal muscle once it has degenerated. It is a noteworthy fact, therefore, that we have in the uterus a tissue in which the actomyosin concentration can be changed at will for the purpose of observing simultaneous alterations in function. This tissue may be a useful experimental material for more general studies than ours. It can be considered, for example, for studies in growth and protein synthesis.

References

1. Csapo, A. *Am. J. Physiol.*, **162**, 406 (1950).
2. ———. *Nature*, **162**, 218 (1948).
3. ———. *Am. J. Physiol.*, **160**, 46 (1950).
4. Csapo, A., and Hermann, H. *Ibid.*, **165**, 701 (1951).
5. Szent-Györgyi, A. *Chemistry of Muscular Contraction*, 2d ed. New York: Academic Press (1951).
6. Nommaerts, W. F. H. M. *Muscular Contraction*. New York: Interscience (1950).
7. Reynolds, S. R. M. *Am. J. Physiol.*, **97**, 706 (1931).
8. Frank, R. T., Bonham, C., and Gustavson, R. G. *Ibid.*, **74**, 395 (1925).
9. Csapo, A., and Corner, G. W. *Endocrinology* (in press).
10. *Ibid.*, **49**, 349 (1951).

Manuscript received July 28, 1952.

Comments and Communications

Un-American Activity

We have noted with misgiving the continuation of attacks by a Congressional committee, individual members of Congress, and certain journalists upon the reputation of the new President of the American Association for the Advancement of Science, E. U. Condon, and indeed upon the American Association for the Advancement of Science itself. May we take this opportunity to express our vigorous disapproval of such attacks, and our concern about the political climate which makes them possible?

We wish also to commend your organization and its officers for their long history of active championship of the cause of scientific freedom.

The American Society for Pharmacology and Experimental Therapeutics, Inc.
Carl C. Pfeiffer, *Secretary*
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Pain—Controlled and Uncontrolled

The stimulating article by Henry K. Beecher, entitled "Experimental Pharmacology and Measurement of Subjective Responses" (Science, 116, 157 [1952]), seems to us to require some extension. It is important to avoid overemphasis upon a single aspect of the study of pain; to wit, action of analgesic agents. Such studies, although of recognized practical importance, are not broad enough to encompass the analysis of the total pain experience.

We enthusiastically endorse Beecher's thesis that man's *subjective response must be used* for the study and the evaluation of pain sensation. It is perhaps a truism to say that one cannot study pain by avoiding it, yet methods of study that are directed at obtaining "objective data" about pain are nearly always experiments that attempt to avoid the *sine qua non* for pain studies—the sensation of pain itself. Beecher unfortunately falls into this trap and contradicts himself by saying in his article that "the chief field of usefulness for experimental pain methods may be in animals," after having emphasized that pain must be evaluated by the subjective response in man.

We consider arbitrary and confusing Beecher's emphasis on the dichotomy "experimental" pain—that produced by measured noxious stimuli in the laboratory—and "real" or "pathologic" pain—such as postoperative wound pain. He states that he has developed a successful method for the study of the latter, but implies that no one has been able to study "experimental" pain successfully and to relate such studies to the suffering patient.

In our monograph *Pain Sensations and Reactions* (Baltimore: Williams & Wilkins), we define the "pain experience" as the individual's integration of all the effects of noxious stimulation and pain. These include (*a*) reactions to the threat of pain prior to actual contact with a noxious stimulus; (*b*) reactions to the noxious stimulation, locally at the site of stimulation, and at the cord and brain stem level (segmental), where integration of important responses begins—i.e., flexor reflexes, neurohumoral, cardiovascular, and other responses; (*c*) the sensation of pain itself, which is integrated at suprasegmental levels, together with accompanying sensations such as pressure, fullness, warmth, cold, etc.; and (*d*) reactions to pain sensation, as, for example, in certain religious rites and in behavior patterns involving masochism and sadism.

These responses are closely interdependent, and it is obvious that pain sensation itself is only a part of this constellation and bears somewhat the same relation to it that vision does to graphic art. It would be only the extreme aesthete who would insist upon limiting the study of vision to the art gallery. *Pain sensation must be separated from associated reaction patterns* if progress is to be made, which Beecher recognizes and then waives.

It is not of basic importance as regards the production of pain whether tissue damage results from specific types of stimulation used in the laboratory or from a surgeon's scalpel. But it is extremely relevant to the individual's pain experience, and the investigator must appreciate which aspect of this experience he is interested in exploring. The study of pain sensation *per se,* never easy, can often be most profitably pursued when the implications of the pain are not a major factor, as, for example, when the thermal radiation method is used. Pain *sensation* is far more difficult to investigate when an individual is extremely frightened, inattentive, obtunded, prostrated, "sick," or exhausted. On the other hand, these would be ideal circumstances for the assay of an agent designed to make the patient "more comfortable." The bedside method is the only one that will ultimately establish whether a given analgesic has a place in clinical medicine. On the other hand, the separately studied effects of an agent on the pain threshold, pain intensity, and reactions to noxious stimulation, local and general, are of vital interest to the investigator and therapist.

Beecher has a system of careful controls for testing analgesics at the bedside and through statistical analysis has been able to rate the effectiveness of various agents in producing postoperative comfort. For postoperative purposes it is important and sufficient to know that, after a given operative procedure, a chemical agent can make the patient more comfortable and afford sleep. Such data, however, are nonspecific; hence their usefulness is at best limited. For example, it cannot be assumed that the information obtained from postoperative pain will apply equally well to pain of labor.

In short, Beecher holds that "pathologic" pain be studied as a unitary phenomenon, whereas in our laboratory and clinical studies there have been developed methods for ascertaining pain threshold, assaying pain intensity, defining pain quality, and appraising reactions to pain. The effects of analgesics upon these variables have been described. In addition, the nature of the adequate stimulus for pain has been clarified—i.e., the production of destructive reactions in tissue at a rate above the ability of the cell to compensate. It would thus appear to be a mistake for investigation to be limited to a single approach to so complex an experience as that of pain. Rather, new and vigorous attacks should be made on the problem at different levels, keeping in mind always that answers obtained by each such attack will throw light upon only a few aspects of the pain experience. It may be argued that a synthesis of these separate components into the "pain experience" is difficult, but the practical importance to the physician in controlling the various aspects of the pain experience is unquestioned.

Finally, we feel compelled to comment upon Beecher's failure with the thermal radiation method for measuring pain threshold in obtaining satisfactory measurements of pain threshold-raising action following administration of analgesics. He states that in his laboratory he "was completely unable to differentiate between 15 mg of morphine and 1 ml of normal saline, so long as he (the operator) was kept in ignorance of which agent the subjects had had." It is not surprising and, indeed, to be expected, that he should find that the pain threshold was raised by both placebo and morphine. It has been repeatedly demonstrated that placebo agents, by virtue of their suggestive effect, strikingly modify pain thresholds and may simulate the effectiveness of an active analgesic. This is in keeping with the common observation that patients suffering from effects of serious tissue damage may be dramatically comforted by placebos. Furthermore, it is of interest to note that the dose-response curves for morphine, obtained by Beecher from his bedside observations, are like those published earlier in our own studies on pain threshold-raising action. According to Beecher, "it is widely stated by those who use experimental pain methods, that aspirin has no analgesic power." As a matter of fact, in our hands the pain threshold-raising effect of aspirin has always been demonstrable when the most rigid controls have been used, including studies in which neither the operator nor the subject knew whether an active agent or a placebo had been administered. Others, including ourselves, have failed to obtain, after aspirin, significant alterations of pain threshold with tests upon untrained subjects. These disagreements show the importance of care and experience in planning studies on pain and in the operation of pain threshold measuring equipment.

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I AM pleased, of course, that Dr. Hardy, Dr. Wolff, and Miss Goodell have taken the trouble to comment in detail on my article in SCIENCE, where I attempted to describe necessary controls for the study of subjective responses. I am only mildly surprised that they have focused entirely upon pain, even though this was, as stated in the article, one of 27 subjective responses we had studied.

There is good reason to dwell upon the problem of pain: both they and we have had our principal experience with this response. There is a further practical reason: I wrote the article in the hope of persuading some of those who study subjective responses, in particular analgesia, and the effectiveness of analgesic agents, to consider a little more fully than in the past, the need for and the nature of, the necessary controls. Analgesics constitute only one aspect, albeit a very important aspect, of the pain problem. We have used pain and its relief as valid material for study of the *general* problem of controls in this field. We have worked slowly and cautiously. Until the essential controls are sharply and clearly established, any work is perilous. One cannot establish universals from a limited experience, of course; but our experience with pain stood us in good stead in study of the other subjective responses mentioned. On the basis of our total experience to date, the generalizations recorded in the article appeared to be justified. I can say to Dr. Hardy, Dr. Wolff, and Miss Goodell that I had no intention of emphasizing analgesics, or even pain, in my article. I thought that was evident.

It is no more possible to study pain broadly and soundly without studying its relief than it is to study sleep without studying wakefulness (*cf.* Kleitman). Many kinds of attacks on the complex pain problems are, of course, possible and desirable. Much of our work has been concerned with measuring pain in terms of its relief. This is indirect, to be sure; biology and chemistry are shot through with equally indirect techniques—for example, the simple determination of the acidity of a solution by the quantity of standard alkali it takes to neutralize it is indirect. It seems rather extreme to call our procedure "studying pain by avoiding it." If this is what we have done, we make no apology for doing so. The technique has been fruitful.

As far as this goes, Dr. Hardy, Dr. Wolff, and Miss Goodell have time and again used their method as a means for studying analgesic agents. It is puzzling to me, and it seems paradoxical, too, that they emphasize "the sensation of pain itself" as presumably elicited with their method and yet use this for the study of analgesic agents. At the same time they stress, rightly, that the *reaction* to pain is an important component of the experience. It is plain that the reaction of the man in a sickbed, where his pain may be a warning of disaster, will not be the same as the reaction of a well and comfortable man in the laboratory subject to a momentary pricking sensation. There are, certainly, traps in the forest.

Dr. Hardy, Dr. Wolff, and Miss Goodell have always attached importance to the reaction to pain as a fundamental part of the process, just as we have done. Since this reaction depends in large part upon its meaning to the subject—a meaning certainly influenced by its origin (whether disease or trauma, on the one hand, or the laboratory, on the other)—it seems to us reasonable to separate pain on the basis of its origins and significance to the subject; that is, experimental or pathological. I am surprised that they found this rather obvious point a "confusing . . . dichotomy."

I should have supposed that we had made clear enough the reasons for our objections to the method of Hardy, Wolff, and Goodell. It did not work in our hands. Admittedly, this might or might not be relevant. We did not rest on our own experience. We enlisted the help of a responsible investigator who had worked happily with the method for years and had published a number of articles based upon it. When he repeatedly failed to distinguish between a large dose of morphine and a placebo (as long as he was in ignorance of what had been used), there did not seem to us to be any point in looking for subtleties with the method—as for example, trying to distinguish between two analgesic agents. Nor did we leave matters here; we went to a number of investigators in the fields of pharmacology and physiology, men who are well known for their painstaking skill in experimentation and sound critical judgment. They *all* reported that their experience had been exactly like ours with the Hardy-Wolff-Goodell method. I certainly have no intention of trading on their names. We discovered them with only a little inquiry. I recommend that Dr. Hardy, Dr. Wolff, and Miss Goodell ask the same questions.

With this background, and for the other reasons stated in our published papers, we became skeptical of the usefulness of experimental pain methods in man for the evaluation of analgesic agents. There is nothing contradictory in our statement that the experimental pain method *may* have some usefulness in animals for a study of pain sensation, but this is outside our own experience. Investigators like Nathan B. Eddy have found experimental pain methods useful in animals for evaluating analgesics, and we defer to their experience. But I wish someone would explain to me how these methods work, when all the experimental pain methods in animals depend upon reflex depression, and yet one can hardly understand how, in the doses used, the analgesics can depress reflexes. There is an interesting problem here. This does not deny that some help may be obtained from animals, but man remains the animal of necessity for the final evaluation of subjective responses.

Hardy, Wolff, and Goodell say that "pain sensation must be separated from associated pain reaction patterns." I heartily agree that this is desirable, but I doubt that it has been done as yet. They have confused this doubt of mine (reasons for it are stated above) with a denial of its importance. Of course it is important, but I have seen no convincing evidence that it has been done or, for that matter, that it can be done.

In their last paragraph Hardy, Wolff, and Goodell appear to make the astonishing suggestion that the reason we failed to use their method successfully was because of the well-known effectiveness of a placebo in treating pain. We have dwelt upon this fascinating fact time and again, but if their method does not distinguish between a large dose of morphine and a placebo, where can one depend on it?

I should like to close by commenting on a matter that seems to me to be fundamental. We are firmly convinced that dependable information free from bias in this difficult field can be obtained only when *neither the subject nor the observer* knows what has been used. Now, when others have failed to confirm their work (as with aspirin, for example), Hardy, Wolff, and Goodell have for years insisted that their success where others failed was due to the fact that they used a few highly trained, experienced subjects over long periods. As everyone knows, the analgesic drugs produce a number of subjective responses which may or may not be related to pain relief—euphoria, for example, "giddiness," and so on. In other words, highly experienced subjects who know in general that they are involved in studies on analgesics are certainly not unaware when a narcotic is used and when a placebo is used. They know all too well what responses are expected. In short, I do not believe it is possible to fulfill the essential requirement of the unknown technique with such drug-wise, sophisticated subjects. This is not by any means to impute dishonesty to them. I would not trust data obtained by myself or by any other observer who knew what was used. Dr. Hardy, Dr. Wolff, and Miss Goodell evidently now also subscribe to the importance of the "double-blind" experiment (see their last paragraph). I doubt if they can achieve it with their highly trained, drug-wise subjects. The investigator I referred to above got good elevation of threshold when he knew morphine was used. He got no dependable data when he did not know what was used.

The highly trained subjects used by Hardy, Wolff, and Goodell came to have a vested interest in the outcome. To be sure, learning on the part of the subjects is always a hazard, but far more so with the group just mentioned than with a group that does not know what to expect, who have no interest in how the data come out, and who are discontinued as subjects after a few doses of the drugs.

It is absolutely essential that unconscious bias be eliminated here. Subjects who know how to recognize the subjective sensations of analgesics and who have an interest in the outcome cannot be considered as unbiased. I am obliged to continue to question the validity of any such experiments when either the subject or the observer is aware of what was used.

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Book Reviews

Science and the Social Order. Bernard Barber. Glencoe, Ill.: Free Press, 1952. 288 pp. $4.50.

It is one of the anomalies of our time that in a period of history when science is markedly influencing the social order this book is probably the first complete study of the subject. Robert K. Merton discusses in his foreword the reasons for the strange neglect of this field. The natural scientists are still, by and large, uninterested in the social sciences, and the social scientist has been afraid to speak of the natural sciences in which he has not been trained. A third factor that may have retarded this study is the fact that for some time the subject was almost monopolized by writers who accepted the Marxian analysis of history.

The book collects under one cover, and in a very readable style, the bulk of what is known on the mutual interaction of science and society. It attempts to correlate the material on the basis of techniques and concepts that have proved of value in other areas of sociological thought.

Barber's conclusions are very tentative—as they should be on the basis of so little established data. Only at the end, where he discusses the role and feasibility of the social sciences, does he become eloquent in defense of his field. His defense is convincing except on one point. He seems to underestimate the possibility of misuse of the social sciences on the basis of his statement that human beings will not let themselves be made into utter automatons. But great suffering can be caused long before this stage is reached, and it requires continual vigilance and a knowledge of what science can and cannot do, if we are not to acquiesce in programs labeled "scientifically established," when in fact scientific knowledge is applied to inhuman ends.

The book begins with a discussion of the nature of science and devotes an all too brief chapter to the sociological basis underlying the historical development of science. The major part of the book then deals with contemporary science both in liberal and authoritarian societies, and specifically with the social organization of science in America in the universities, in industry, and in government. A chapter on the respective roles of the individual and society in the progress of science makes fascinating reading, followed by the most provocative part of the book, deal-