used the method, successfully, he said, over a period of years, and found that as long as he knew what the subject had received, he could reproduce fine dose-effect curves; but when he was kept in ignorance, he was no more able than we were to distinguish between a large dose of morphine and an inert substance such as saline.

This observation of 19 years ago has now been confirmed by 14 other groups both in Europe and in this country (*1*). The curious fact was thus well established that experimental pain as then produced in man did not respond dependably to morphine or other powerful analgesic agents, whereas pain of pathological origin always responded in greater or lesser degree. During this same period it was also established that modifications of the Hardy-Wolff-Goodell method when applied to animals were useful. The situation was indeed puzzling.

In 1964, Smith, Egbert, Markowitz, Mosteller, and I (*3*) decided to take up once again the problem of tourniquet pain. (Previous attacks in our laboratory and elsewhere had failed.) We had long thought that possibly one difficulty with experimental pain methods was that the pain produced is usually sudden and fleeting—"pricks," "jabs," "stabs of pain"—whereas most clinical pain, aside from some of the colics, is much more sustained. As a matter of fact, it is difficult to control with drugs colicky pain or the pain aroused by sudden motion of a wound. There was the suggestion in these observations that study of slowly developing and sustained pain might be of considerable interest for experimental purposes.

Our current method is based on tourniquet pain which is accented by a brief period of exercises of the hand and arm below the tourniquet, followed by a rest period during which the individual focuses on his pain. The pain is categorized at five levels: 0 = none, 1 = slight, 2 = moderately distressing, 3 = very distressing, and 4 = unbearable. In our studies the pain increased progressively after cessation of exercise of the hand and arm. The tourniquet was not removed until the subject reported his pain was "unbearable." The time required to effect this varied from 3 to 47 minutes. Using well-established, properly designed techniques we found, in comparing morphine with placebo, that morphine consistently tended to allay the development of pain at each of the four levels, but satisfactorily significant ($P < .001$) alleviation occurred only at levels 3 and 4. It finally was clear that really severe pain in man, even though it is experimentally contrived, will respond to morphine in a smooth, dependable fashion.

It then became apparent that the difficulty with earlier experimental pain methods was that they focused on "threshold values." This concept of the importance of the threshold seems unquestionably to have been responsible for getting the whole experimental pain study problem off the tracks. Attention has now been focused on the more severe levels of pain and one now can get satisfactory dose-response data. (Incidentally, a reexamination of other kinds of data derived from "threshold" values might well be carried out in the light of the above.)

This finding, now well established, is important in two respects: practically, there is great need for a method of appraising in man, conveniently and accurately, the effectiveness of new pain-relieving agents. There is great need for a method which will not require the tedious use of pathological pain. Thus, the present findings appear to have wide usefulness to the pharmaceutical industry.

More interesting, perhaps, are the philosophic connotations which lead to a more accurate insight into the factors involved in pain production and pain relief. These factors have been discussed in detail elsewhere (*1*). The presence of true anxiety, a state not readily produced by earlier experimental methods involving fleeting pain, appears to be of great importance. Whatever the reasons, it is evident that there are qualitative differences between threshold pain (it does not respond dependably even to large doses of narcotic) and severe pain.

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Visual Excitation of Blood Clotting

In a recent report by George Wald (*1*) the main theme is a comparison of amplification in blood clotting and in visual excitation, the comparison being based on the "cascade of proenzyme-enzyme transformation" which was suggested by Macfarlane (*2*) and Davie and Ratnoff (*3*) as a possible mechanism in blood clotting. Wald makes clear that "such an enzyme cascade . . . remains only an unsupported suggestion in visual excitation." That it has been "to a degree established in the mechanism of clotting" seems to me to attribute stronger foundations to the idea than can now be claimed for it. In my own view, it would be better described as the product of speculative imagination. The work did not take into account all relevant data in the literature. In a critique (*4*) on the complicated construct of proenzyme-enzyme cascade sequence, I have shown that the basic data on the chemistry of prothrombin activation are against the generalization. The principles involved in prothrombin activation function as autocatalytic feedback systems. Autoprothrombin C alone is all that is needed to generate thrombin activity (*5*), and all else, such as lipids, Ac-globulin, and calcium ions is in support of that reaction.

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