STUDIES ON PAIN. MEASUREMENT OF THE EFFECT OF MORPHINE, CODEINE, AND OTHER OPIATES ON THE PAIN THRESHOLD AND AN ANALYSIS OF THEIR RELATION TO THE PAIN EXPERIENCE

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Though valuable observations have been made of the action of analgesic agents, these have been based in the main on animal experimentation and clinical impression (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11). No adequate method for assaying their effects on the pain threshold in man has been available. However, since the prime purpose of an analgesic drug concerns its action in man, it is desirable to measure accurately its effect on man's pain threshold. For such measurement a suitable method has now been developed (12). Also, it is important to define precisely other analgesic effects. It has thus been possible to evaluate the therapeutic effectiveness of the opiates, and to make inferences concerning the nature of the pain experience in man.

METHOD

Quantitative measurements of the pain threshold were made by exposing 3.5 cm.^{2} of skin surface for 3 seconds to thermal radiation. The intensity of radiation which barely evoked pain was denoted as the pain threshold. In this way the normal pain threshold level was established to ± 2 per cent by making observations at 5-minute intervals until a constant threshold was obtained. This usually required four observations. After the control measurements an analgesic agent was administered and observations of the pain threshold were made at 10-minute intervals until the threshold had returned to the control level, that is, until all pain threshold-raising action had ceased. The height of the pain threshold-raising effect was expressed in per cent elevation above the control level. The protocols were distributed so that the threshold of each subject was measured by a colleague who in turn was unfamiliar with the change in his own threshold. Occasionally, observers not participants in the experiment made threshold readings. Thus, three independent protocols were made, no individual knowing how much his own threshold had been altered. Occasionally sterile salt was introduced into one of the syringes so that it was known to all that one of the subjects had not received an analgesic drug, although which one had been so treated was not revealed until the end of the experiment. All agents were administered intramuscularly.

With each pain threshold reading the subject made a concise statement of his psychological state. In the 10-minute interims between readings the subjects sat comfortably and engaged in reading, writing, or conversation. Sleep was not permitted for reasons to be discussed later, and if drowsiness became difficult to manage the subjects walked about the laboratory. During long experiments food was taken, but not until it had generally been conceded that the peak of action had been passed. The 3 subjects then consumed about the same amount of milk and bread. This usually took no longer than 15 minutes, after which the readings continued as before.

Morphine in various amounts was administered to each subject on 18 different occasions and codeine on 15. Thus, a total of 54 morphine and 45 codeine experiments was performed on 3 subjects. The time interval between such experiments was seldom shorter than 1 week and usually 2 weeks or more. Thus the possibility of acquiring a tolerance to morphine and codeine was minimal. Furthermore, it was demonstrated by a repetition of standard quantities about once a month that no tolerance to morphine had been developed. At the end of the study the threshold-raising effects of 15 mgm. of morphine and of 60 mgm. of codeine were the same as at the beginning of the study. In addition, experiments were made with other opium derivatives, namely dihydromorphinone ("Dilaudid"), methyldihydromorphinone[1] ("Metopon"), pantopium hydrochloride ("Pantopon," Roche), and combinations of scopolamine and morphine.

SUBJECTS

The subjects studied were the 3 authors of the paper. They represented both sexes and different body types. One of the males was a tall, linear person, the other shorter, more muscular and "thick set." The woman was tall and well developed. All weighed about the same, *i.e.*, 65 kgm. The 3 individuals resembled each other in the possession of more than average energy and curiosity but differed from each other temperamentally in life orientation and in interests. They were conscientious witnesses and, as might be expected, in-

[1] Courtesy of Dr. Howard L. Andrews, U. S. Public Health Service.

terested and willing. Since it was necessary to make these determinations on persons who were suffering no pain other than that induced by the experiment, it was unreasonable to expect any but those most concerned to expose themselves to this inconvenience.

OBSERVATIONS

Threshold. In the manner described above, the pain threshold was determined daily and before each experiment. It was found, as has been discussed in detail elsewhere, that the individual's pain threshold varied but little from day to day and also that the pain threshold of the 3 subjects differed but slightly.

During the first series of experiments the subjects were free of all pain other than that induced by the test procedure. Freedom from pain before and during the period of pain threshold measurement is important. It will be shown in the second part of this communication that pain, *per se,* raises the pain threshold and that pre- or co-existent pain, either spontaneous or induced experimentally, seriously alters the threshold-raising action of morphine and codeine. Menstruation, which introduced no factor of discomfort in the female subject, did not change her pain threshold.

The subject's reaction to the experimental procedure was recognized as having potentially important effects upon the observations. In order to evaluate this effect, several experiments were done in which one subject received a placebo. A typical experiment is shown in Figure 1. It can be seen that the procedure itself was neutral so far as threshold-raising effect was concerned.

SERIES I

Morphine sulphate. Observations. The results of experiments with 8 different quantities of morphine from 0.1 mgm. to 30 mgm. are shown in Figure 2. The threshold to pain was observed to rise within 10 minutes following injection.

The height and duration of the threshold-raising effect increased with the amount administered. Whether the amount of the agent was large or small the threshold began to rise after the same interval of time but continued to rise at different rates until the peak effect for the particular amount had been reached.

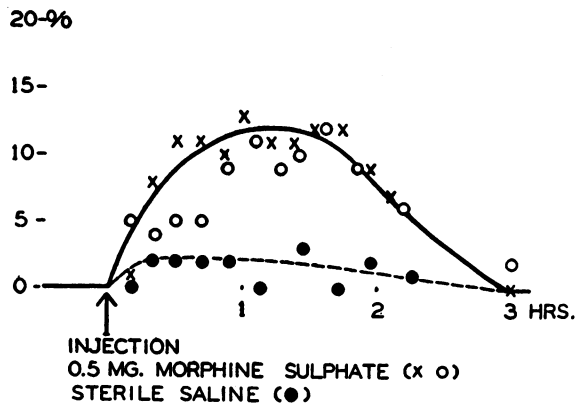

FIG. 1. THE PAIN THRESHOLD-RAISING EFFECT OF 0.0005 GRAM OF MORPHINE SULPHATE ON TWO SUBJECTS

A third subject received sterile saline. Points × and ○ represent the pain threshold elevation after 0.0005 gram of morphine sulphate; ●, the effect of sterile saline. The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect.

As can be seen in Figure 2, when the morphine was given in quantities from 0.5 mgm. to 15 mgm., the peak of action was reached almost at the same time, namely, in approximately 90 minutes. With 30 mgm., however, the peak effect was not reached until 150 minutes after administration. The duration of action from control threshold back to control threshold varied from 3 hours in the case of 0.5 mgm. amounts to somewhat over 7 hours in the case of 30 mgm. amounts. The 0.1 mgm. amount of morphine sulphate was apparently without any threshold-raising action.

Comment. The time-action curves of Figure 2 can be analyzed, as regards the amount of agent given, in three ways:

(*1*) the maximum height of the pain threshold-raising effect, (*2*) the length of the period of effectiveness, and (*3*) the total thresold-raising action of the agent.

The maximum height of the threshold-raising action was obtained from the highest part of each time-action curve.

The length of the effective period was taken to be the elapsed time between the injection and the return of the threshold to the pre-injection level.

The total threshold-raising action of the agent was computed by multiplying the duration in hours of effect by the average per cent above the control

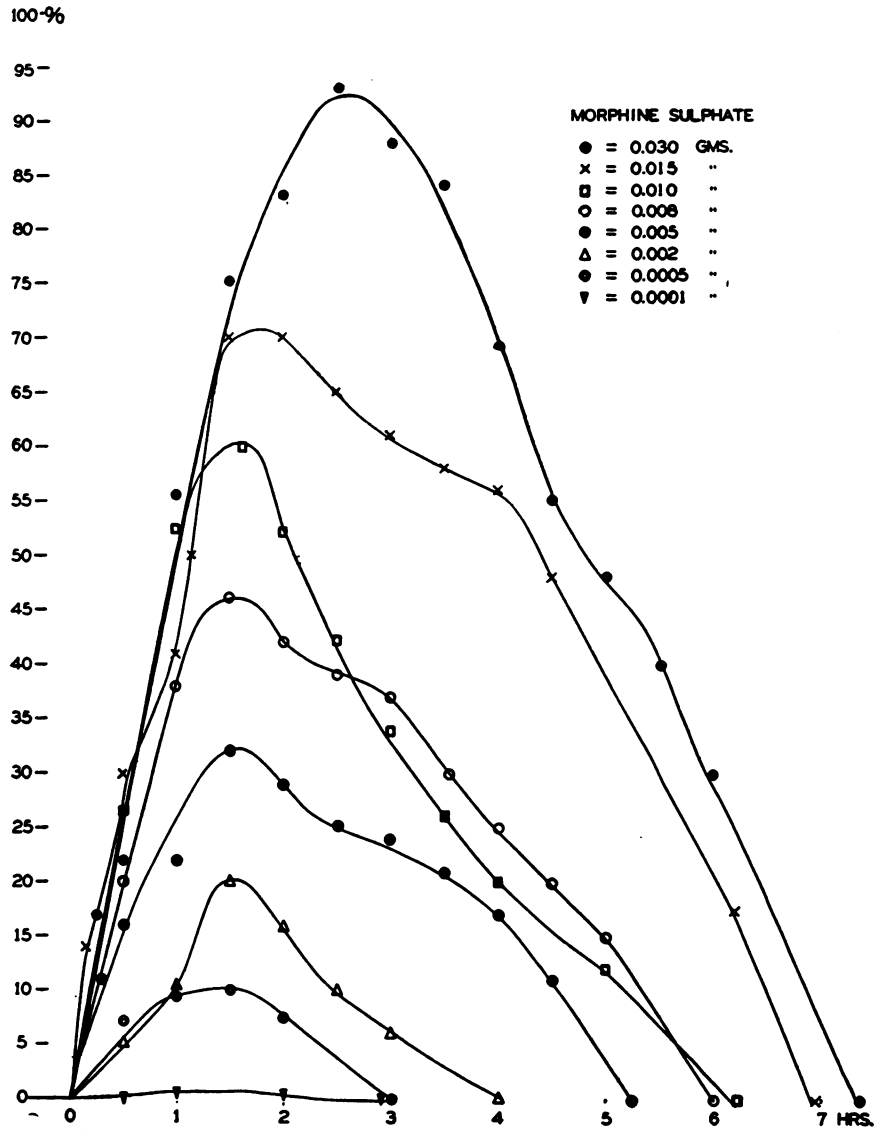

FIG. 2. TIME-ACTION CURVES FOR MORPHINE SULPHATE

Pain threshold elevation after morphine sulphate in quantities of 0.0001 gram to 0.030 gram. The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect. The ○ indicates the time of injection of the morphine sulphate. Each point represents the average of the threshold levels for 3 subjects.

level. The latter figure was derived by taking the average of all the individual percentages represented by points on the curve of Figure 2. This is represented by the area under each time-action curve.

It will be seen (Figure 3) that the maximum analgesic effect in terms of quantity is a straight line function from 0.5 mgm. to 15 mgm. For amounts greater than 15 mgm. the increase in threshold-raising effect with quantity becomes progressively less. Thus, doubling the amount of agent, *i.e.*, from 15 mgm. to 30 mgm., increases the threshold-raising effect less than 20 per cent. The curve in Figure 3 may be considered in three parts: (*1*) The abrupt change in the curve between 0.1 mgm. and 0.5 mgm. suggests that the minimal

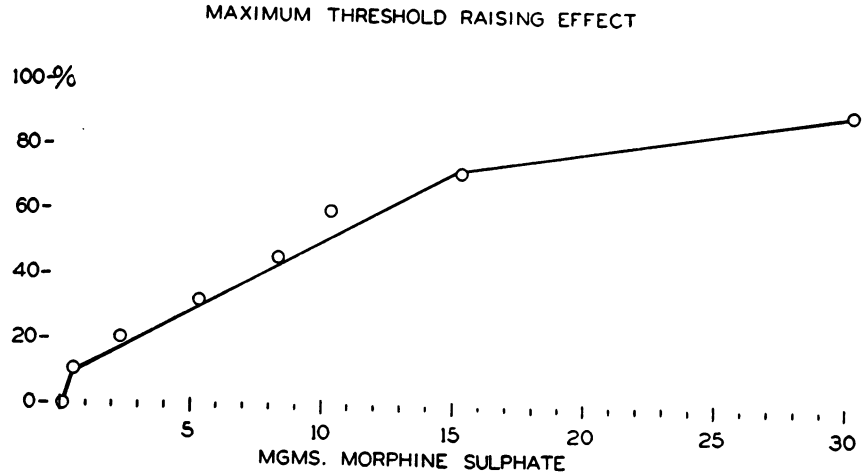

FIG. 3. THE MAXIMUM PAIN THRESHOLD-RAISING EFFECT OF MORPHINE SULPHATE FOR QUANTITIES FROM 0.0001 GRAM TO 0.030 GRAM

The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = quantity of morphine sulphate administered.

effective amount of morphine is approximately 0.5 mgm. (0.007 mgm. per kgm. body weight). It is to be observed that this is less than 1/100 of the minimal effective dose reported by Eddy (6) and his associates (10) who used the cat as a test object. (*2*) The portion of the curve between 0.5 mgm. and 15 mgm. shows the threshold-raising effect to be in direct proportion to amount. (*3*) The latter portion of the curve (beyond 15 mgm.) suggests a condition analogous to a chemical saturation, that is, the effect is not increased by increased concentration of one of the reacting agents. On this basis the "saturation" quantity of morphine sulphate, or the smallest amount with which the highest threshold-raising effect is attained, is close to 30 mgm. The "saturation" level, or the highest threshold-raising effect of which the drug is capable, is 100 per cent above the control threshold. This is in the range of tissue injury and blisters were regularly produced without pain in these experiments. Should increasingly larger quantities be administered, further threshold-raising effect, probably with unconsciousness, could be anticipated. Such amounts, however, were beyond the pharmacological range and the scope of this study.

The duration of threshold-raising effect increases with the amount given from 0.1 mgm. to 30 mgm. (Figure 4). However, the rate of increase with amount becomes progressively smaller so that doubling the quantity from 15 mgm. to 30 mgm. causes only 5 per cent increase in the length of the effective period. This means that 30 mgm. was rendered ineffective almost in the same length of time as 15 mgm. so that the rate of essential elimination must proceed more rapidly with the larger amounts. Again, there is to be observed an abrupt change in the direction of the curve between 0.1 gram and 0.5 mgm., indicating a minimal effective dose between these amounts.

The relation of total threshold-raising action to amount is shown in Figure 5. There was a direct proportion between effect and amount up to 15 mgm. Doubling this amount, however, increased the total action only 25 per cent.

The time-action curves for all amounts studied were of a simple type, that is, the level of the threshold-raising effect rose with time until a maximum was reached and then descended relatively smoothly to the control level. The highest threshold-raising effects for amounts from 0.5 mgm. to 15 mgm. occurred at the same time. The fact that 30 mgm. had its maximum threshold-raising effect 1 hour later than the lesser amounts indicates inhibition of the effective absorption [2]

[2] The words effective absorption are meant to include all the processes occurring between injection and the production of analgesia. Essential elimination is used to mean the rate at which the agent is rendered ineffective as an analgesic.

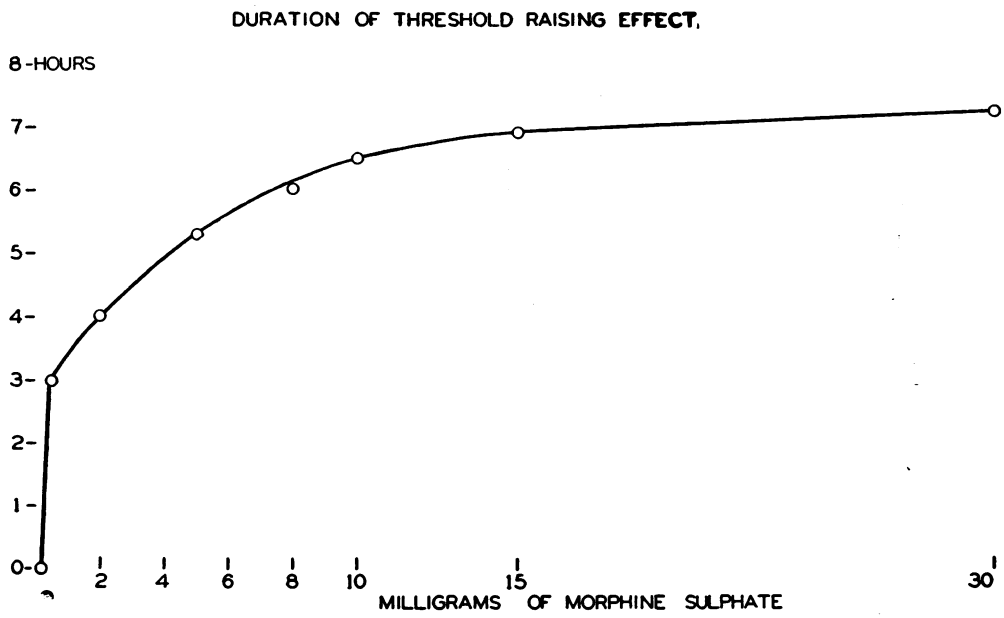

FIG. 4. THE RELATION BETWEEN DURATION OF THRESHOLD-RAISING EFFECT (ORDINATE) AND THE QUANTITY OF MORPHINE SULPHATE ADMINISTERED (ABSCISSA)

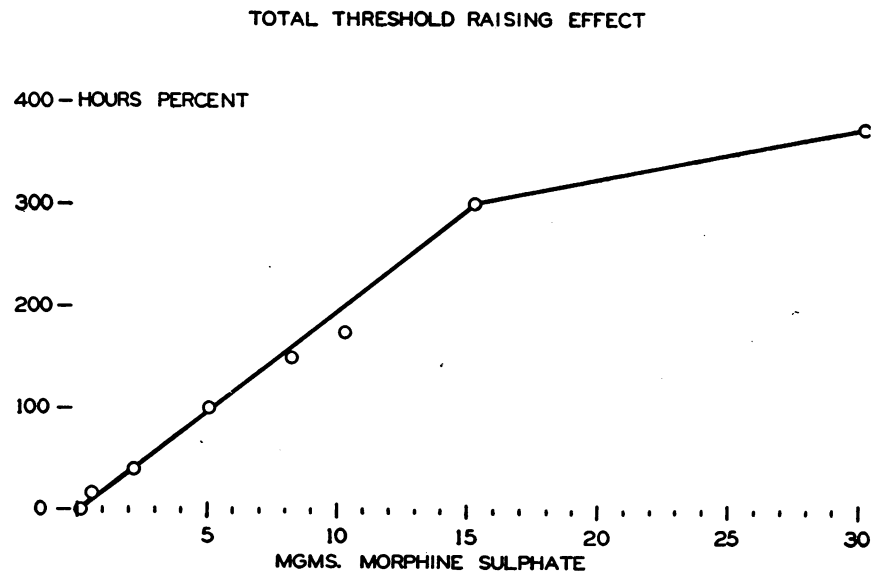

FIG. 5. THE RELATION BETWEEN THE TOTAL THRESHOLD-RAISING EFFECT AND THE QUANTITY OF MORPHINE SULPHATE ADMINISTERED

The ordinate was computed by multiplying the average per cent rise in pain threshold by the hours of duration of effect resulting from a given quantity of morphine sulphate. The abscissa represents quantity of morphine administered.

after the larger quantity. It would appear further that the essential elimination has actually been accelerated in this instance since the effective period of threshold-raising was only 5 per cent longer than that for one-half this amount, or 15 mgm.

Morphine sulphate. Psychological effects; observations. In addition to the rise in pain threshold, the administration of morphine resulted in relaxation, freedom from anxiety, lethargy, apathy, and difficulty in mentation. Outstanding was the freedom from anxiety and feeling of contentment. The pain threshold-raising action was not closely related in time to these psychological changes, the latter effects outlasting the threshold-raising action by many hours.

After the administration of morphine in amounts from 5 mgm. to 30 mgm., the following effects were observed in varying degrees, depending on the quantity given. Within 3 to 4 minutes after the injection the subjects became aware of feelings of muscle relaxation about the extremities, the neck, and the back. This was soon followed, approximately 5 minutes after injection, by changes in mood or attitude. Thus, the subjects before injection were alert and preoccupied with technical problems associated with the progress of the experiment and its successful culmination. After injection all seemed to be going well. Time between readings, which formerly seemed long and tiresome, became short and pleasurable. Loquacity was evident within a half hour after the injection. Conversation was agreeable and steady without push. Anxieties or dilemmas not concerned with the experiment also seemed to be readily soluble, and anticipation of events immediately to follow the experiment was free from conflict. This change in attitude was maintained for the next 2 to 3 hours.

This freedom from anxiety or " contentment " was associated with a constructive attitude toward the problems at hand. Fears, inhibitions, and doubts were reduced. Discriminations and decisions became easier. The mood changes were also described as " good humor," " euphoria," " pleasurable relaxation," and " exhilaration."

After about 30 minutes, attention, retention, and concentration became more difficult as did clear, logical or continuous thinking. Such difficulties in mentation continued for 3 to 4 hours.

Commonly, freedom from anxiety was associated with and followed by apathy. There was an increasing indifference to situations and decisions, with little concern about either difficulties or opportunities. As a manifestation of apathy, the attitude toward vomiting experienced with the 30 mgm. quantities was instructive. The vomiting was repeated and violent and was associated with no more emotional reaction than would ordinarily accompany rinsing the mouth or swallowing.

Lethargy outlasted the above effects and was present often for as long as 24 hours. Toward the end of this time it ceased to be accompanied by a mood which made acceptance or indifference possible. Apparently, in reaction to a decreased effectiveness, the subjects experienced annoyance, impatience, and resentment. Such states became manifest sometimes as soon as 4 hours after injection and persisted for 24 to 72 hours. The extent of the over-irritability was conditioned by the subject's awareness of his defects and by the stress to which he was exposed. When, during this period following the experiment, he was in a relatively neutral environment with few decisions of importance confronting him the mood reaction was of a less distressing nature. When, however, he was confronted with major decisions and either failed to recognize or make allowances for his lowered effectiveness, this period of 24 to 72 hours after the morphine injections was one of increasing tension and depression. Moreover, when the post-morphine period came just before menstruation, depression and tension were sometimes accentuated and prolonged.

Other morphine effects. " Full-headedness " or headache was repeatedly experienced by 2 of the subjects about 5 minutes after the injection. These head sensations were gone within a half-hour, sometimes recurring 12 hours later. Feelings of faintness, and " light-headedness " had their onset and termination within a half-hour of the injection. Unsteadiness of gait was noted within a half-hour of the injection and was short-lived.

Itching of the nose was a complaint of 2 of the subjects. The symptom had its onset between 1 and 2 hours after the injection, and lasted from 2 to 4 hours. Itching elsewhere (pubic region) occasionally occurred.

Dimming of vision associated with reduction in

the size of the pupil was observed within a half-hour of the injection. Slight constriction of pupils without dimming of vision could still be seen 10 to 14 hours after the injection.

Nausea had its onset characteristically within 10 minutes after the injection and with smaller amounts disappeared within a half-hour. After large quantities of morphine it recurred in "waves" for 2 or 3 hours after the injection and with 30 mgm. persisted for 8 hours with vomiting which was repeated and vigorous.

The administration of 30 mgm. of morphine sulphate produced, in addition to the changes described above, a state akin to prostration. Pallor, loss of initiative, nausea, vomiting, sweating, weakness, and unsteadiness of gait were the dominant features. Three mgm. of dihydromorphinone hydrochloride ("Dilaudid") had a similar effect.

Codeine phosphate. Observations. Codeine phosphate was injected intramuscularly in amounts from 15 mgm. to 120 mgm. The time-action curves for this agent are shown in Figure 6. As in the case of morphine sulphate, the maximum threshold-raising effect was reached at approximately the same time for all the aforementioned quantities, *i.e.*, about 90 minutes. The duration of action varied from 3 hours with doses of 15 mgm. to somewhat more than 5 hours after 120 mgm. The minimal effective quantity of codeine was not determined.

Comment. The maximum pain threshold-raising effect of this agent was proportional to the amount administered up to 60 mgm. (Figure 7)

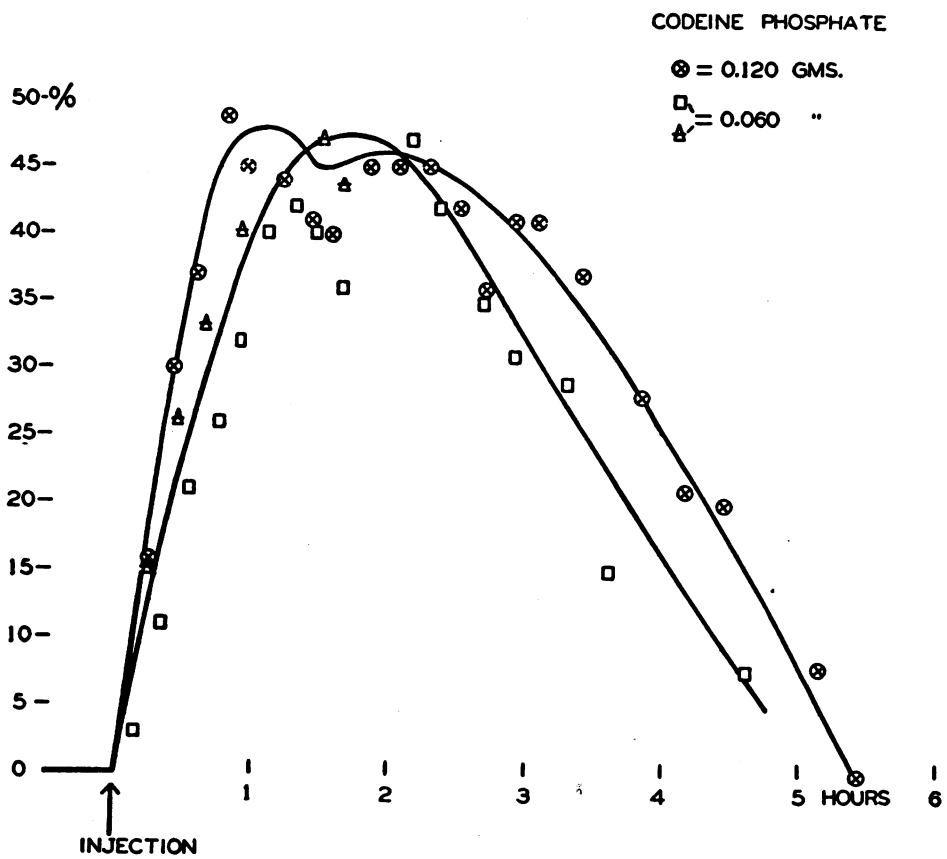

FIG. 6. PAIN THRESHOLD ELEVATION AFTER QUANTITIES OF 0.60 GRAM AND 0.120 GRAM OF CODEINE PHOSPHATE

The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect. Each point represents the average of the threshold level in 3 subjects.

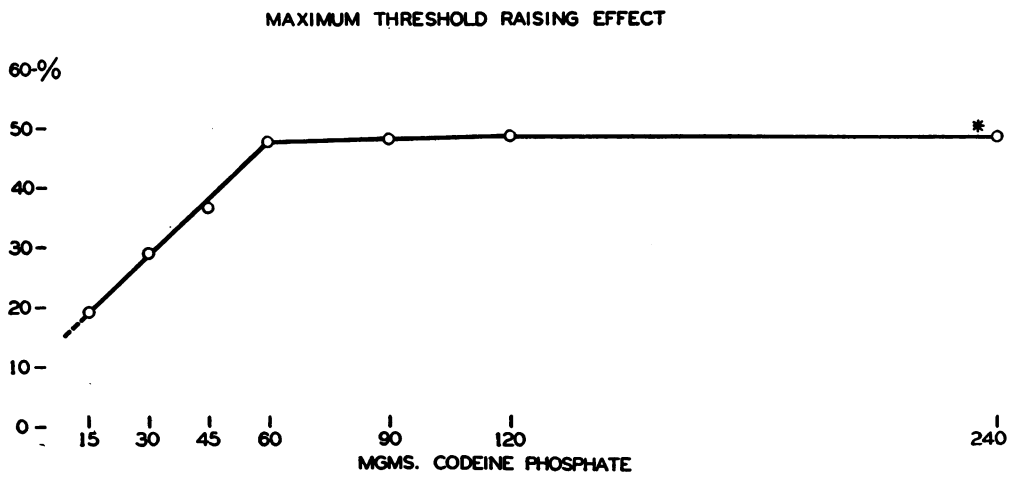

FIG. 7. THE MAXIMUM THRESHOLD-RAISING EFFECT OF CODEINE PHOSPHATE FOR QUANTITIES FROM 0.015 GRAM TO 0.240 GRAM *

The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = quantity of codeine phosphate administered.

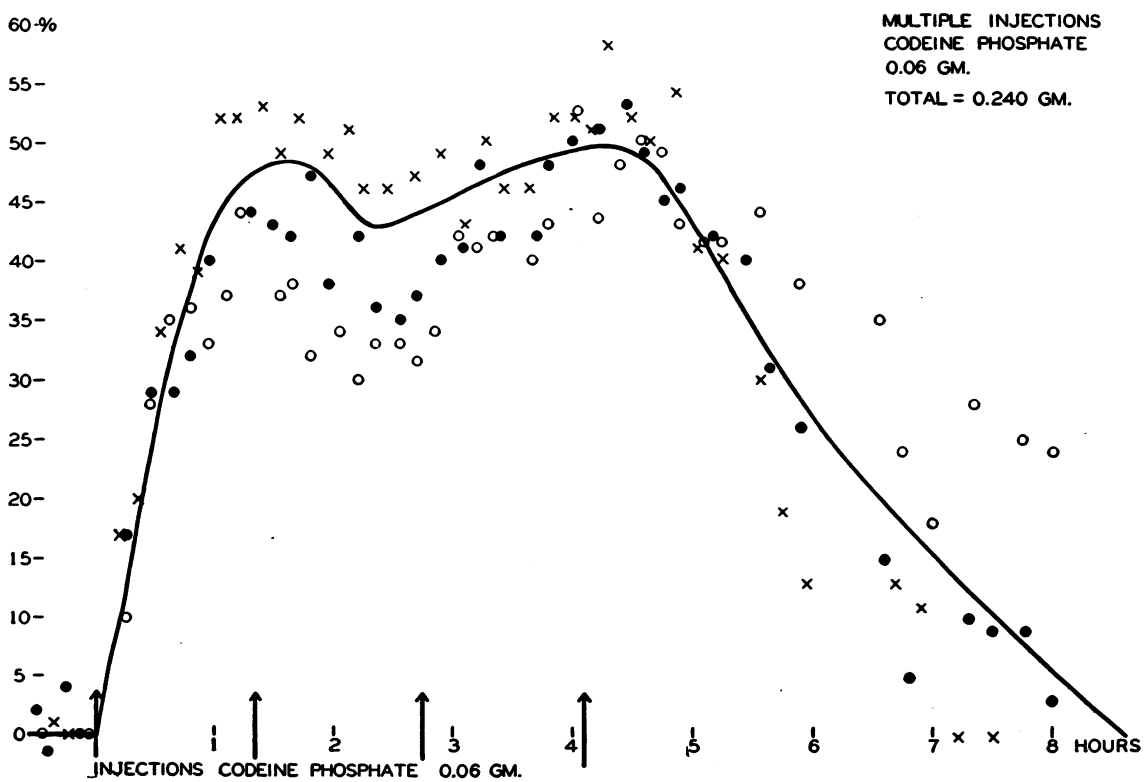

FIG. 8. THE EFFECT ON THE PAIN THRESHOLD OF REPEATED INJECTIONS OF CODEINE PHOSPHATE, 0.060 GRAM, AT 80-MINUTE INTERVALS

The ordinate = per cent elevation of threshold above the control level as zero. The abscissa = duration of effect. The points ●, ×, ○ represent the individual threshold levels in 3 subjects.

* 0.240 gram given in four injections of 60 mgm. each, 80 minutes apart.

(0.92 mgm. per kgm. body weight) resulting in a rise of 45 per cent to 50 per cent above the normal threshold. Administration of double this amount, or 120 mgm., caused no further rise in threshold. Therefore, 60 mgm. may be considered the saturation quantity for codeine and a 50 per cent rise in threshold above the control may be considered its saturation level.

To test the concept of "saturation" level and quantity, the following questions were posed. After the administration of 60 mgm. of codeine phosphate, when the pain threshold had been raised to the established maximum effect of approximately 50 per cent above the control level, would a second injection of 60 mgm. raise the level further? Would the action of the second 60 mgm. start from this high level, or would it have no influence on the pain threshold other than to maintain it at the level which had been reached by the first 60 mgm.?

Observation. Figure 8 shows that despite three attempts to raise the threshold above the previously attained maximum of about 50 per cent through the addition of 60 mgm. of codeine at 80-minute intervals, no further elevation was observed. The threshold-raising effect was not increased beyond that produced by the first 60 mgm. injected. The threshold returned to the control level 4 hours after the last injection.

Comment. The above experiment demonstrates the validity of this concept of a "saturation" quantity and level, and shows that the only effect of additional amounts as regards threshold-raising is to prolong the action. As in the case of morphine, increasingly larger quantities ultimately could be anticipated to have further threshold-raising effect, but again such amounts would be beyond the pharmacological range.

The total threshold-raising action of codeine, shown in Figure 9, increased proportionally up to 60 mgm. Thereafter, increasing the quantity increased the total action far less. Moreover, vomiting and prostration were experienced with 120 mgm.

Figure 10 shows the relationship between the duration of action and quantity of agent. Although the data are not so regular as they are for morphine, the relationship between these factors

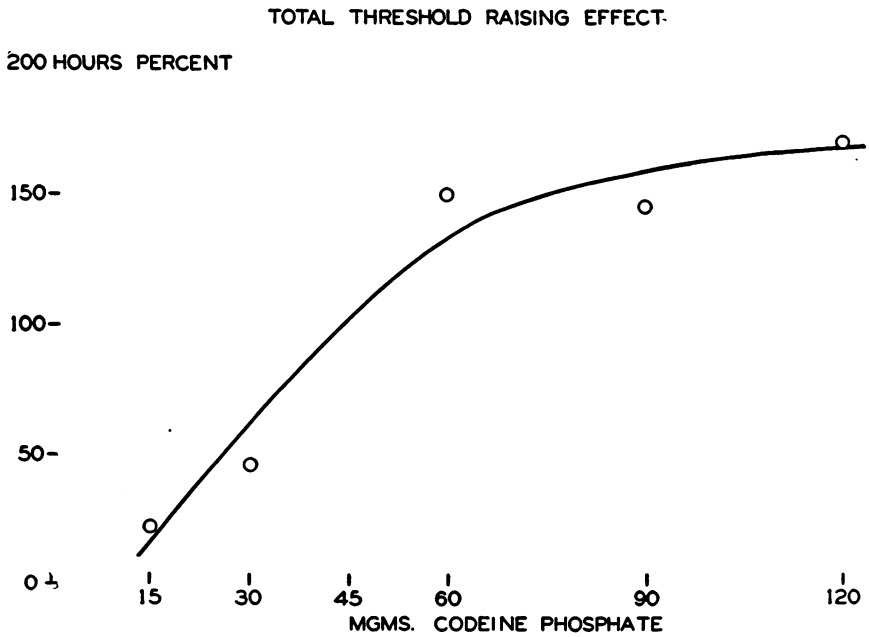

FIG. 9. THE RELATION BETWEEN THE TOTAL THRESHOLD-RAISING EFFECT AND THE QUANTITY OF CODEINE PHOSPHATE ADMINISTERED

The ordinate was computed by multiplying the average per cent rise in pain threshold by the hours of duration of effect resulting from a given quantity of codeine phosphate. The abscissa represents the quantity of codeine administered.

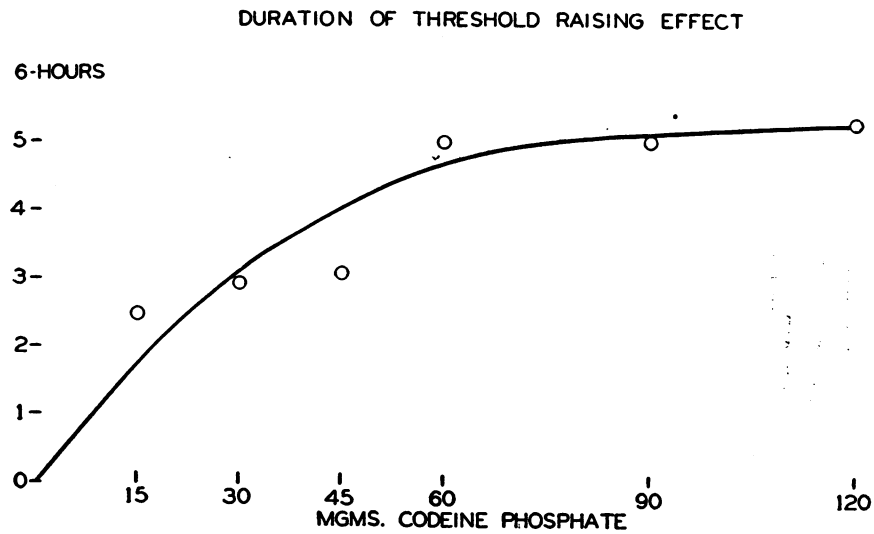

FIG. 10. THE RELATION BETWEEN DURATION OF THRESHOLD-RAISING EFFECT (ORDINATE) AND THE QUANTITY OF CODEINE PHOSPHATE ADMINISTERED (ABSCISSA)

is similar. For codeine the "saturation" quantity is approximately 60 mgm.

Inspection of the time-action curves for morphine and codeine reveal: (*1*) The height of threshold-raising action which can be obtained with codeine is limited to about one-half that of morphine. (*2*) The time-action curve of analgesia for morphine sulphate revealed that essential elimination increased at a constant rate with quantities up to 15 mgm. However, with larger quantities of the agent there was acceleration of the rate so that duration of effect with 15 to 30 mgm. of morphine was about the same. The time-action curve of threshold-raising for codeine phosphate revealed essential elimination at a constant rate up to 60 mgm. With larger amounts within the range here studied, there was acceleration of the rate, as in the case of morphine. (*3*) The psychological effects produced by morphine and codeine are qualitatively similar, although morphine is capable of producing greater effects than codeine.

Eddy (6) and his co-workers (10), on the basis of most painstaking studies, have compared the action of various opiates with one another upon cats. Thus morphine was said to have ten times greater analgesic action than codeine. Such a statement unfortunately does not indicate the difference in the degree of threshold-raising that can be induced by the two agents with different amounts as assayed here. For example, in man 2 mgm. of morphine raised the pain threshold 20 per cent, whereas it required 15 mgm. of codeine to raise the threshold a similar degree. Again, 60 mgm. of codeine were necessary to raise the threshold 50 per cent, whereas only 8 mgm. of morphine were required. On the other hand, 15 mgm. of morphine raised the threshold 75 per cent but no amount of codeine within the pharmacological range can raise the threshold to a degree equal to 15 mgm. of morphine. It may be that the discrepancy between these results and those of Eddy is centered about the difference in sensitivity of the methods of assay.

Several other well known derivatives of opium and combinations were tested to determine if they possessed more effective pain threshold-raising qualities or other advantages over morphine or codeine.

Dihydromorphinone hydrochloride ("Dilaudid" (Bilhuber Knoll)). Three mgm. of this agent (*7*) were given intramuscularly to 2 subjects. The psychological effects were pronounced and the pain threshold-raising action dramatic. At the peak of its action the threshold was raised somewhat over 100 per cent (Figure 11). This effect was approximately the same as that observed after the administration of 30 mgm. of morphine.

Lethargy was pronounced and there was repeated vomiting. The psychological effects were

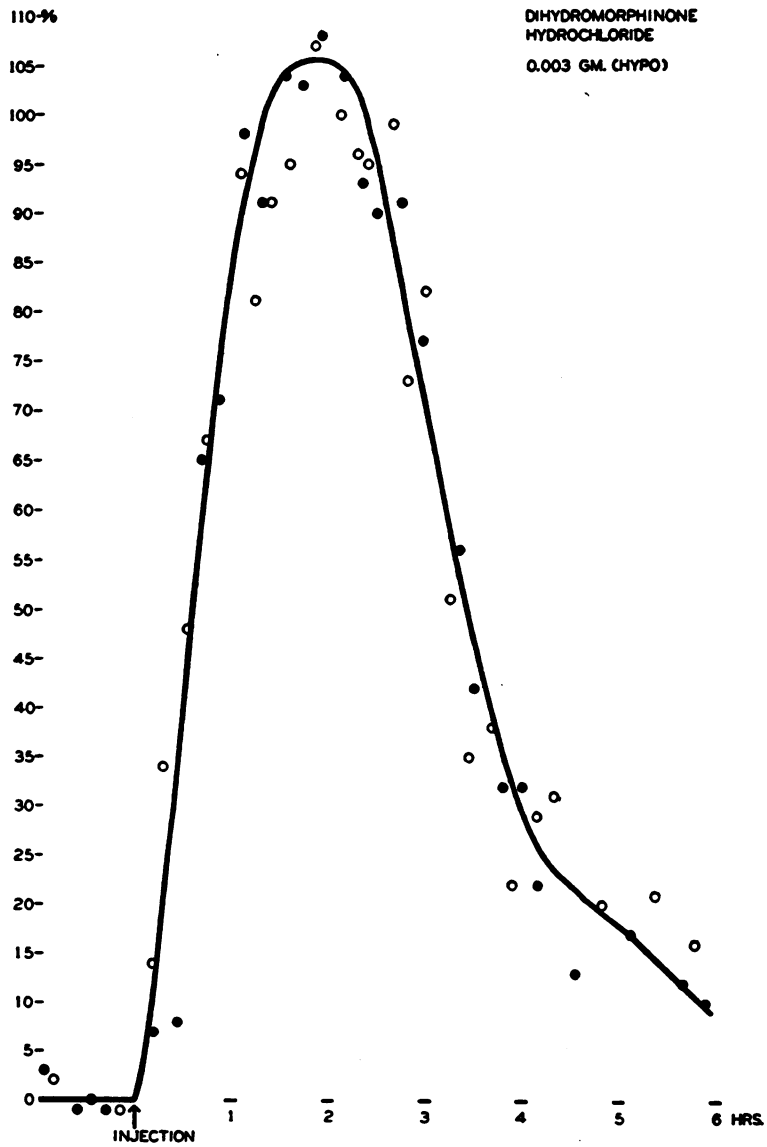

FIG. 11. THE PAIN THRESHOLD ELEVATION RESULTING FROM THE ADMINISTRATION OF 0.003 GRAM DIHYDROMORPHINONE HYDROCHLORIDE ("DILAUDID")

The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect. The points ○ and ● represent the threshold levels in 2 subjects.

little different from those experienced after 30 mgm. of morphine sulphate.

Pantopium hydrochloride (*"Pantopon"* (*Roche*)). Twenty mgm. of "Pantopon," given intramuscularly, raised the pain threshold about 35 per cent and the duration of the effect was 5 hours (Figure 12). Many of the common psychological and physiological effects of morphine were encountered. The threshold-raising action of 20 mgm. of pantopium was equivalent to about 8 mgm. of morphine sulphate.

Methyldihydromorphinone (*"Metopon"*). The injection of 6.6 mgm. of methyldihydromorphinone (11) had a threshold-raising action which

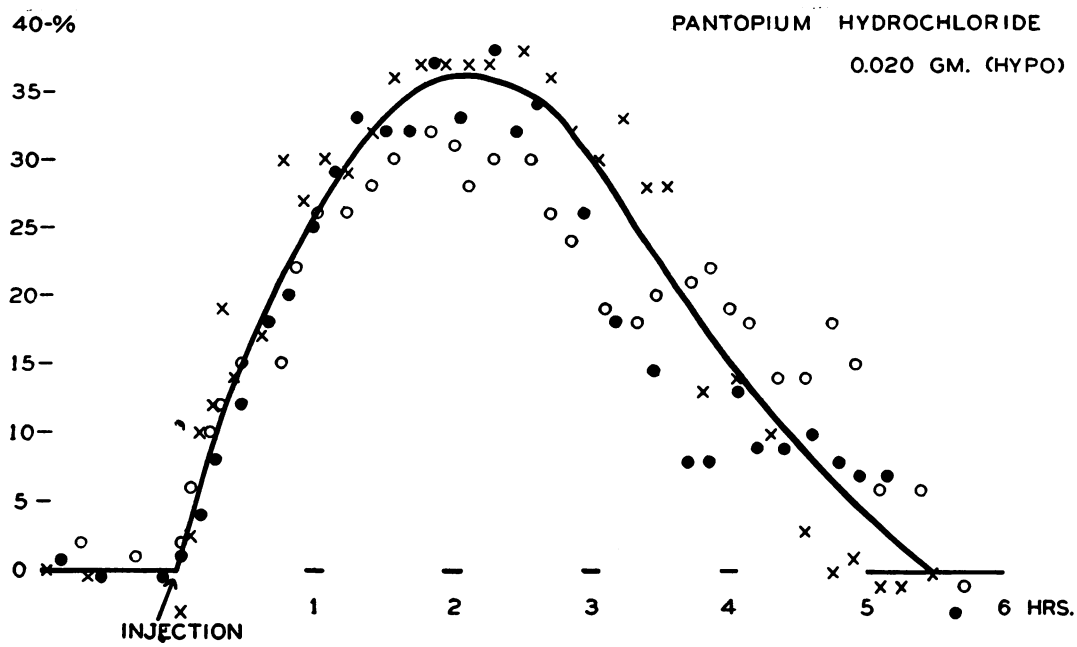

FIG. 12. THE PAIN THRESHOLD ELEVATION RESULTING FROM THE ADMINISTRATION OF 0.020 GRAM PANTOPIUM HYDROCHLORIDE ("PANTOPON," ROCHE)

The ordinate = per cent elevation of threshold above the control level as zero. The abscissa = duration of effect. The points ○, ×, ● represent the individual threshold levels in 3 subjects.

was comparable to approximately 30 mgm. of morphine sulphate. The peak effect was attained in about 90 minutes and remained at a level of approximately 90 per cent above control threshold for 1½ hours, after which the threshold gradually lowered, reaching the control level in about 7 hours after administration (Figure 13).

Vomiting began 2 hours after injection and occurred intermittently for the next 2 hours. Constriction of the pupils was noted within 10 minutes of the injection and persisted for at least 10 hours. The symptoms of prostration, as described with 30 mgm. of morphine, were present.

Psychological effects were first manifested within 10 minutes of the time of injection. They began with feelings of "light-headedness," relaxation, and fullness in the head. The freedom from anxiety and feelings of contentment bordering on euphoria, characteristic of morphine, soon followed. Time sense was shortened. The mood alteration persisted for about 2 hours, after which followed lethargy and a state bordering on prostration. As demonstrated by the ability to retain numerals, concentration and retention were disturbed. Four hours after the injection there was still lethargy and indifference to intermittent vomiting. The subjects were unable to differentiate these effects from those which were experienced with 30 mgm. of morphine sulphate or with 3 mgm. of dihydromorphinone hydrochloride ("Dilaudid"). However, the sequelae of methyldehydromorphinone were of shorter duration, and 24 hours after the injection no after-effects were noted.

Morphine with scopolamine. The combination of morphine sulphate and scopolamine hydrochloride (in amounts of 8 mgm. and 0.4 mgm., respectively) was injected intramuscularly. The pain threshold-raising effect of morphine was not increased nor was the duration of action prolonged as a result of the addition of scopolamine. Indeed, the pain threshold-raising effect was less than was obtained with an amount of 8 mgm. of morphine sulphate alone. All the usual physiological and psychological effects of morphine were present and the following appeared in excess: dry mouth, unsteadiness of gait, difficulty in accommodation, dry smarting eyes, difficulty in mentation, and lethargy. The combination may have assets as regards the induction of sleep or relaxa-

tion but its threshold-raising action is not superior to that of morphine alone.

Comment. The inferences from these experiments concerning the assay of threshold-raising effects of opium derivatives might be criticized on the basis that they represent the action upon only one type of pain, namely, superficial pain with its burning, tingling, prickling, or "bright" quality and that they may not be valid for deep pain of the aching or cramp variety. Such a criticism is unjustified since the results obtained from deep pain induced by a balloon that distended the duodenum were not unlike those described above. The similarity between the effect of drugs on these

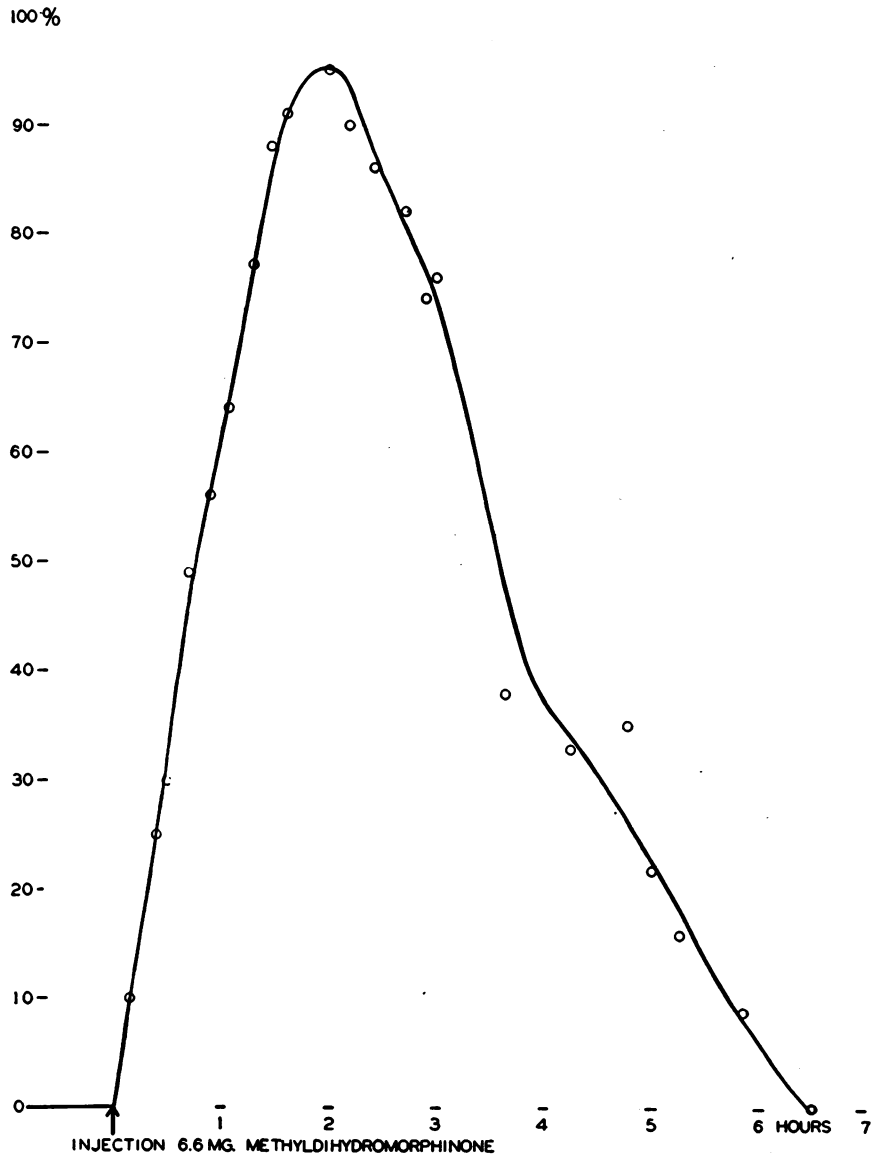

FIG. 13. THE PAIN THRESHOLD ELEVATION RESULTING FROM THE ADMINISTRATION OF 6.6 MGM. METHYLDIHYDROMORPHINONE ("METOPON")

The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect. Each point represents the average of the threshold levels in 3 subjects.

two types of pain indicates that the results described would hold equally well for all types of pain.

SERIES II

The aim of the first series of experiments was to demonstrate the threshold-raising action of morphine and its more important derivatives. The experiments were done with as few complications as the situation permitted, and pain and sleep were especially avoided. In the following experiments prolonged pain was introduced as a variable since in this way the action of morphine could be appraised more nearly in terms of its common therapeutic use.

Method. In the manner described above the pain threshold was measured in the 3 subjects. To introduce a uniform stimulus of pain the following method was adopted. A sphygmomanometer cuff was applied over the upper arm and inflated to 200 mm. Hg pressure. It was left in this position for 40 minutes. The subjects contracted the muscles of the arm slightly and about the same amount. A gradually increasing, deep, aching pain resulted from such ischemia which began about 12 minutes after circulatory occlusion and continued for the remainder of the period, becoming progressively worse. The pain was described by the subject in terms of intensity from 1 to 6+. Six + and 8+ were considered intolerable pain. When the cuff was removed there followed 3 minutes of intense tingling and "pins-and-needles" sensations in the arm and hand. This terminated the painful experience.

To obviate the inference that the threshold-raising effect was due to the metabolic by-products of such circulatory occlusion, pain was produced by two other methods. The first of these produced pain by submersion of an extremity in ice water (3° to 5° C.) for as long as the pain persisted, then withdrawing and experiencing the pain which followed such submersion. One extremity after the other was immersed in this manner for a total of 40 minutes. The pain was intense and almost continuous.

The second method consisted of swallowing a catheter to which was attached a balloon which was distended with water when it reached the duodenum. The balloon was distended until a considerable pain resulted, which was then maintained for 40 minutes.

The third method was to compress the trapezius and biceps muscles by screw clamps and by manual compression until intense, deep, aching pain resulted. It was necessary to readjust the clamps from time to time. By means of such readjustments and manual compression an intense pain was maintained for 40 minutes. The pain induced by all of the above four methods had qualitatively similar effect on the threshold-raising action of morphine. The methods differed from each other in the intensity of the pain which they induced, and in the quantitative effect on the morphine action.

After the control readings, which preceded the morphine injection, the painful procedure was begun: (*1*) 46 minutes before injection; (*2*) 1 minute after the injection; (*3*) 50 minutes after the injection; (*4*) 120 minutes after the injection. Pain-threshold readings were made every 10 minutes throughout the subsequent 6 to 7 hours. The results were as follows:

Observations. Morphine sulphate. Pain induced early during the threshold-raising action of morphine and codeine altered the effect and the duration of the action. The longer the interval between the injection of morphine and the induced pain, the less effect was there upon the threshold-raising action of the agent. On the other hand, if the pain was induced just before or just after the injection of morphine the effect upon the subsequent threshold-raising action was dramatic.

In Figure 14 is represented graphically this effect of the introduction of pain on the pain threshold-raising properties of morphine sulphate. Pain was produced in four experiments by a cuff wound around the arm as described above. In the fifth experiment, pain was produced as follows: In subject H. G. W. by muscle clamping; in subject J. D. H. and H. G. by ice water; and in subject H. G. by duodenal distention. The heavy black line represents the pain threshold-raising effect of 15 mgm. of morphine sulphate in 3 individuals without pain. By contrast, it is shown that a pain of approximately 40 minutes' duration, introduced immediately before injection, (curve 5), reduced the pain threshold-raising properties of the drug to an almost negligible amount, *i.e.,* to average maximum effects of 7 to 12 per cent in 6 individual experiments; if introduced at the same time as the injection, the effect was shortened as indicated in the curve 4. The curve 3 shows the effect when pain was introduced 50 minutes after injection, and the curve 2 shows the effect when pain was introduced 2 hours after injection of morphine, when the threshold-raising action of the agent was at its peak. Pain reduced the intensity and duration of the previously described psychological effects.

Comment. It may be seen that pain introduced immediately before or after the morphine injection had greater effect on its pain threshold-raising action than that introduced later after the pain threshold had been raised.

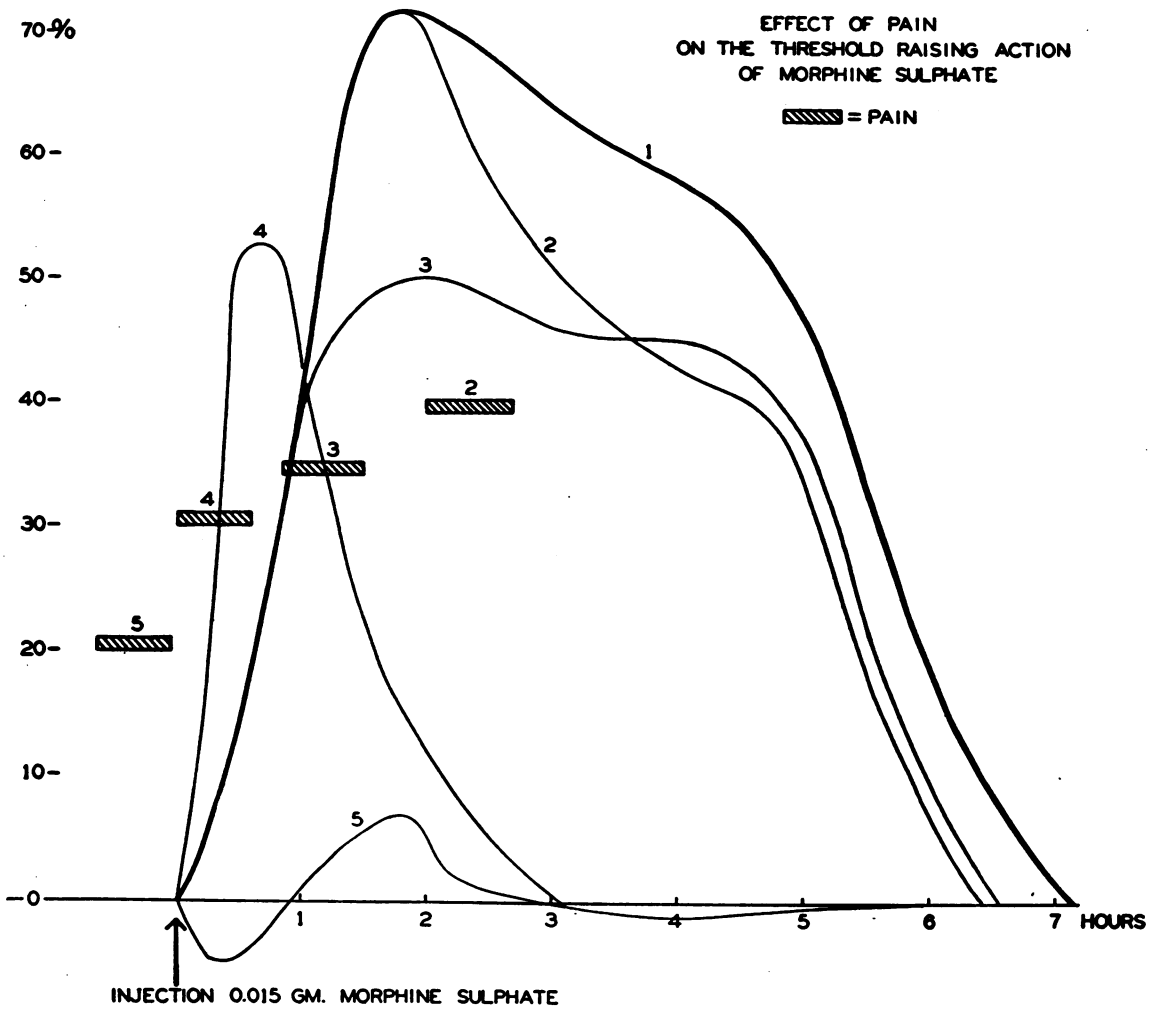

FIG. 14. THE EFFECT OF SUSTAINED PAIN (40 MINUTES) ON THE PAIN THRESHOLD-RAISING PROPERTIES OF MORPHINE SULPHATE (0.015 GRAM)

The heavy black line, 1, represents the pain threshold-raising effects of 0.015 gram of morphine sulphate in 3 subjects without pain. The lighter lines and blocks represent the following: 2. Pain 120 minutes after the injection. 3. Pain 50 minutes after the morphine injection. 4. Pain immediately following morphine injection (after 1 minute). 5. Pain preceding and ending 6 minutes before the morphine sulphate injection. The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect. Each curve represents the average of the threshold levels in 3 subjects.

The reduced effect of the pain on the time-action curve when introduced after the threshold had been raised could not have been due to the fact that the subjects at this time perceived the pain to a lesser degree. Subject H. G. reported a 6+ pain from the manometer cuff inflated 120 minutes after injection, whereas H. G. W. and J. D. H. reported only ½ to 1+ pain. The effect of the procedure upon the time-action curve was exactly the same in all three instances.

The time-action curves of morphine shown in Series I revealed two characteristics: (*1*) a period during which the morphine is being absorbed by the central neuronal pain mechanisms resulting in gradual elevation of the pain threshold; (*2*) the gradual elimination of threshold-raising action. As the same painful procedure is more effective in reducing the threshold-raising action the sooner it occurs in relation to the time of morphine injection, one may infer that the essential absorption is affected more than the essential elimination. In other words, if the morphine has had an oppor-

tunity to exert its influence upon nerve cells, the pain changes the time-action curve far less.

Observations. Codeine phosphate. Pain had a similar impeding effect upon the pain threshold-raising action of codeine phosphate. The above described (cuff method) experience of pain was introduced shortly after the injection of 120 mgm. of codeine phosphate. The threshold-raising effect of this quantity of the agent, as shown in Series I of this communication, was slightly over 50 per cent at its peak, with the threshold maintained near the 50 per cent level for about 2 hours, and gradually returning to the control threshold in about 6 hours after administration. After pain, the threshold had returned to the control level in from 2 to 3 hours (Figure 15). The application of a cuff to the other arm in 1 subject for a second 40-minute period immediately following the first had no further detectable effect on the pain threshold-raising action of codeine. As in the case of morphine, pain reduced the intensity and duration of the characteristic psychological effects.

Comment. It is to be noted in Figure 15 that, with the introduction of pain 9 minutes after the injection of codeine, the threshold-raising effect is probably the result of the induced pain rather than the codeine since, as has been shown before, pain has such an effect upon the pain threshold. The initial effect of the codeine during this hour, therefore, cannot be determined directly from this experiment. However, the subsequent threshold-raising effect was curtailed, as seen in the swift descent of the curve back to threshold level in 3 to 4 hours.

Morphine sulphate and codeine phosphate reacted similarly to the occurrence of pain during

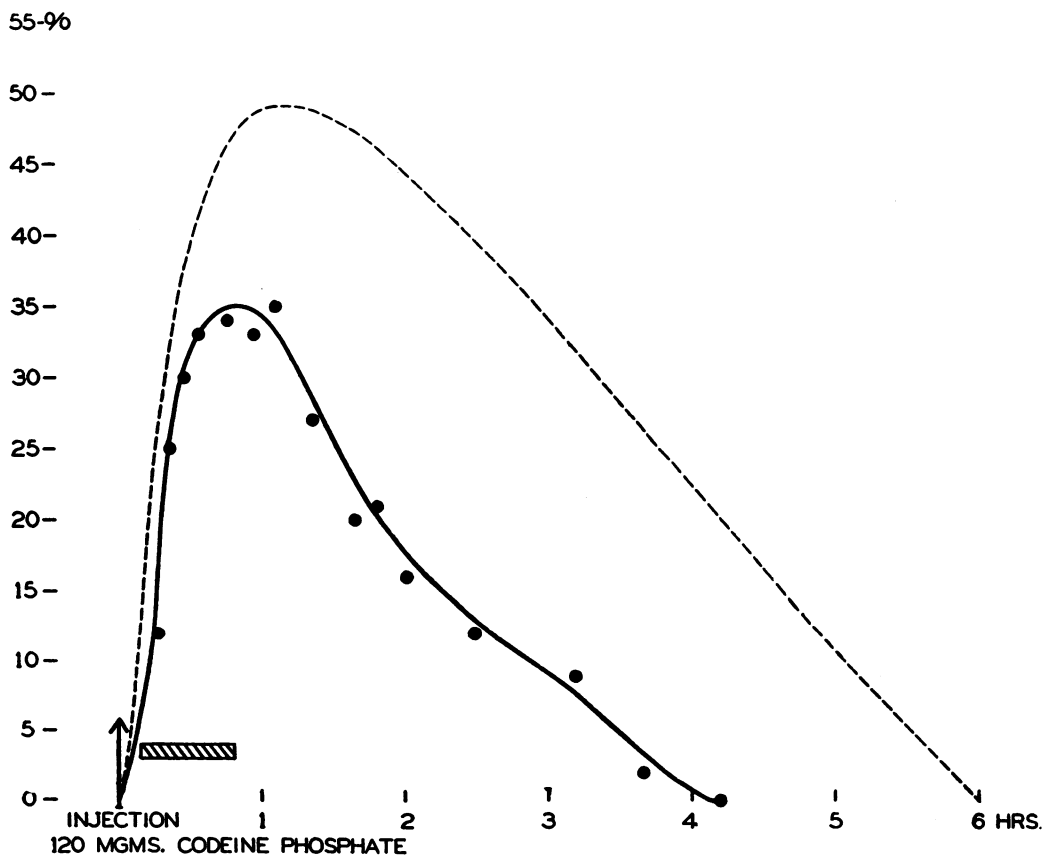

FIG. 15. THE EFFECT OF SUSTAINED PAIN (40 MINUTES) ON THE PAIN THRESHOLD-RAISING PROPERTIES OF CODEINE PHOSPHATE

The ordinate = per cent elevation of pain threshold over the control level as zero. The abscissa = duration of effect. ▨ = sustained pain (40 minutes).

their cycle of action. It appears that there is a mutual antagonism between pain, and the derivatives of opium. That is to say, if the pain precedes the introduction of the agent, the analgesic action of the latter is limited or obliterated whereas, if pain is introduced after the threshold-raising effect has reached its peak, *i.e.,* about 90 minutes after the injection, the effect of the pain is less evident.

Further analysis of pain as antagonist of morphine and codeine analgesia. Since the experience of pain is associated with increased sympathetic activity, and presumably increased epinephrine output (13), it was considered desirable to appraise the action of epinephrine upon the threshold-raising action of morphine. It is appreciated that epinephrine liberation would be but one of many effects of pain, but it is one that lends itself to experiment.

Observation. Three subjects in two experiments received 10 mgm. of morphine in the first experiment and 15 mgm. in the second experiment. Two hours before the administration of morphine, 1 cc. of 1 : 1000 epinephrine (" Adrenalin," Parke Davis) was injected subcutaneously in one experiment and intravenously in the other. The latter was given as 300 cc. of a 1 : 300,000 solution of epinephrine during 1 hour. Although blood pressure and pulse effects of the epinephrine had disappeared at the time of morphine injection, the subjects still felt " tense and excited."

The effect on the threshold-raising action of 15 mgm. of morphine is seen in Figure 16. The well-defined threshold-raising action of 15 mgm. of morphine was completely obliterated in 2 of the 3 subjects. In the third subject, the threshold, instead of being raised about 70 per cent by 15 mgm. of morphine, was raised only 25 per cent. This occurred in the heaviest of the 3 subjects in whom the adrenalin had the least effect as regards feelings of tension and excitement. The psychological effects of the morphine were also reduced in intensity and duration. Similar effects were noted in the experiment after 10 mgm. of morphine.

Comment. It is likely that the action of epinephrine in offsetting the morphine effects was on the central nervous system since even traces of circulating adrenalin show themselves in pulse and blood pressure alterations. In these subjects at the time of morphine injection no such effects were observable. On the other hand, effects arising from central stimulation, namely, feelings of tension, exhilaration, and excitement, were present. It is conceivable, therefore, that there had been some change in the state of the central pain mechanism as a result of the previous epinephrine injection, making it refractory to the threshold-raising action of morphine.

The influence of pain and epinephrine on the pain threshold-raising action of morphine and codeine was not specific in the sense that analgesia alone was reduced or obliterated. Indeed, all of the detectable morphine effects were less pronounced and of shorter duration. However, the threshold-raising properties of morphine and codeine were profoundly disturbed by pre- or coexisting pain, and more so than that action responsible for the altered emotional state. Such effects as freedom from anxiety, contentment, and relaxation, though less pronounced, were still clearly evident. This differential effect made it appear as if pain had selected one function of morphine and spared the others.

Such central actions of epinephrine, or agents like it, are not without analogy since sympathomimetic agents are known to reduce the effect of anesthetics (14, 15).

The nature of the pain experience and its bearing on the action of morphine and its derivatives. The data thus far considered present an apparent contradiction: (*a*) the analgesic action of morphine and codeine was reduced or obliterated by pain; (*b*) morphine and codeine undoubtedly reduce the distress experienced during pain. These seemingly contradictory observations can nonetheless be reconciled.

To begin with, consideration of the data necessitates a formulation of pain which will include the two aspects of the pain experience.

1. *Pain perception.* The perception of the sensation of pain is to be differentiated from the reaction pattern to pain. Pain is a sensation that differs from all others, having its own neural apparatus and physiological properties and recognizable because of its unique esthetic qualities.

2. *The reaction pattern of pain.* The reaction pattern of the organism to the sensation of pain usually follows promptly the perception of pain.

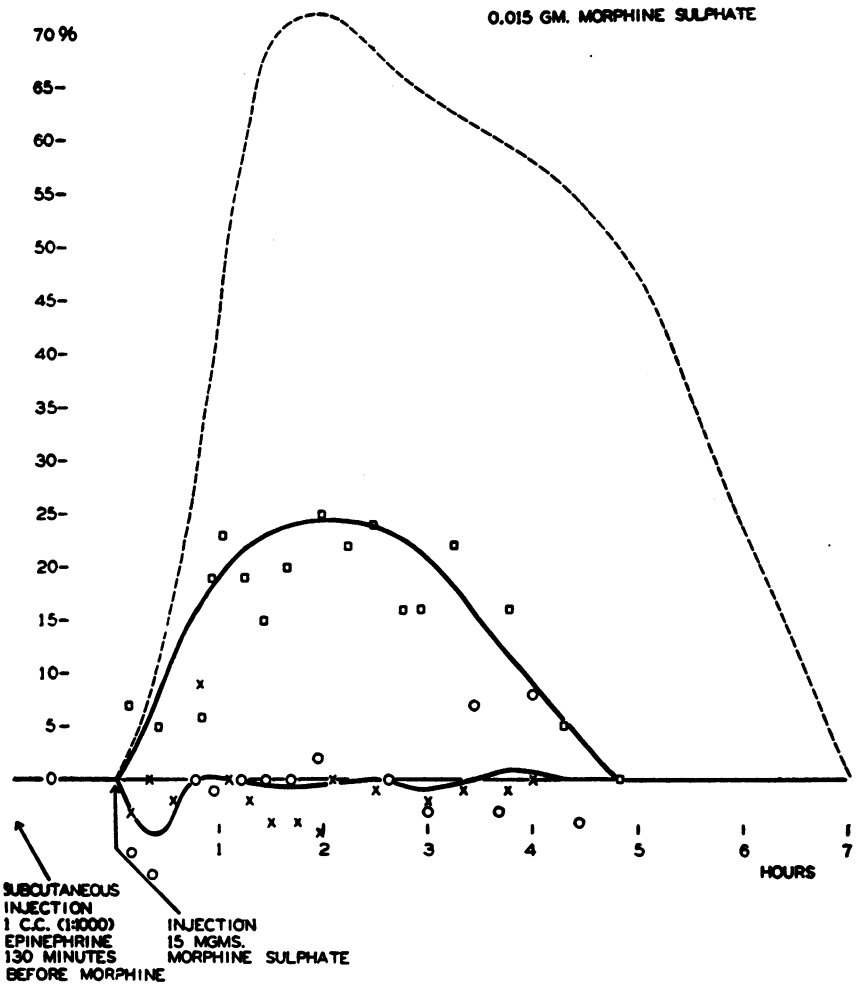

FIG. 16. THE EFFECT OF THE ADMINISTRATION OF EPINEPHRINE ON THE PAIN THRESHOLD-RAISING ACTION OF MORPHINE SULPHATE

Dashed line = effect of 0.015 gram of morphine sulphate in the absence of epinephrine. Solid lines = effect of 0.015 gram of morphine sulphate after epinephrine administration. The points ×, ○, □ represent the individual threshold levels in 3 subjects.

It has many components, including emotional, smooth muscle, gland and skeletal muscle expressions. The reaction pattern is, however, independent of perception and may be dissociated from it. It may, moreover, be modified or even obliterated.

It is the second of these aspects of the pain experience which will be further considered here. A pattern of withdrawal, flight, fight, and anxiety has become closely attached to pain perception. The perception of heat, sound, or cold resembles pain in that they are sensations which have associated with them a pattern of response. However, the pattern of reaction to pain is unlike the pattern of reaction to sound, heat or cold in that it is more stereotyped, more predictable, and thus less readily recognized as capable of being dissociated from perception. However, there is a genuine distinction between perception and the accompanying reaction pattern. Such distinction is apparent and is easy to comprehend when the response is not stereotyped, as for example the responses to light, touch, heat, cold, and smell. But when, as in the case of pain, there is an inborn

as well as a further elaborated stereotypy developed from experience, the contrast between perception and reaction may not be so apparent.

The effect upon the subjects' attitude toward pain when it was induced for experimental purposes, without morphine, is relevant. Outstanding facts concerning the pain in these experiments were: A realization that it could be terminated immediately if desired, satisfaction in the completion of a certain period of pain for the sake of the successful outcome of the experiment, and appreciation that tissue injury was minimal and that there would be no untoward sequelae from the pain experienced. In other words, the attitude toward the pain was one of relative relaxation, interest, and satisfaction because of its experimental significance. There was complete freedom from anxiety. Hence, very painful procedures could be tolerated with relative impunity. After such prolonged periods of pain, the subjects experienced lethargy, drowsiness, or relaxation that could readily have been followed by sleep.

Other instances of similar dissociation of pain perception from the pattern of reaction to pain are seen in the following:

1. The indifference to injury sustained during the excitement of games or combat.
2. The absence of reactions to pain when, during the influence of suggestion, hypnosis or catalepsy, tissue is injured.
3. The apathy or " quietism " that accompanies tissue damage during autosuggestion and during religious and mystical practices.
4. The indifference to tissue damage during sexual excitement.
5. The indifference to pain often witnessed during parturition in women who are confident in their physician and desirous of bearing a child.

Such a dissociation of perception of, and reaction to, pain may be of many varieties with varying degrees of completeness. Further, the individual may or may not be aware of such dissociation. For example, in our experimental procedure there was complete awareness of pain as a sensation, although it was largely dissociated from reaction. In contrast, during combat one may even be unaware of pain sensation as well as free of pain reaction. There may be more or less denial of pain reaction with repression of vocalization or flight, yet with many other visceral reactions to pain, including syncope. In other words, the reaction to pain may be dissociated from perception in many ways. Distinction between the two is essential to an understanding of the pain experience.

Let us consider now the contribution made by opium and its derivatives to our understanding of these dual aspects of the pain experience. Morphine, for example, has at least two actions: (*1*) it impedes to a greater or lesser degree the perception of pain; (*2*) it detaches the perception of pain from the fight-flight-anxiety so closely attached to it. It is this aspect of the morphine experience which is variously described, but which is the common denominator of almost everyone's experience during its action. Thus, freedom from anxiety, contentment, apathy, and indifference about time are common experiences. Not only anxiety but pain itself no longer arouses feelings of distress. The pain sensation is perceived and is recognized as pain with no difficulty, but as a result of the morphine action there does not follow thereon the old and well-established reaction pattern to pain. In short, the opiates dissociate pain perception from the reaction pattern.

Experimental data present other instances of such dissociation of perception from reaction (16). For example, a dog after considerable training developed a fixed response to a strong negatively conditioned stimulus, a metronome beat, which had never been accompanied by food. After repeated presentation it elicited zero salivary response, in contrast to a bell which had always been associated with food and which called forth 200+ cm. of saliva. Five minutes after the strong negatively conditioned stimulus (the metronome), had been presented, the dog was exposed to the stimulus of a flashing electric light which had heretofore been constantly accompanied by food but which was a weak positively conditioned stimulus. When presented by itself, it elicited a moderate salivary reaction, 150+ cm. of saliva. Now, however, when offered so soon (3 minutes) after the strong negative stimulus, the salivary reaction pattern to the light was abolished and there was no saliva. Four minutes later the light elicited again 142 cm. of saliva. There is no doubt that the stimulus was perceived by the dog because with the flashing light the ani-

mal turned its head and body toward it. In other words, although the animal had perceived the light, the perception was dissociated from the reaction which that stimulus usually evoked.

It is possible that in an analogous manner, after morphine administration, the subject exposed to pain perceives the pain sensation, although the pain has been dissociated from the reaction pattern which that stimulus evokes. The organism is therefore in a state that allows perception, perhaps almost as complete as that before the administration of morphine, but which prevents the pattern of reaction from assuming its completed form. It is for this reason, possibly, that patients exposed to severe colic pain often state that the pain after morphine is not gone but that it seems to have no significance.

Further evidence that the threshold-raising effect of morphine can be dissociated from other morphine effects is offered by the cat. It has been shown by Eddy and his associates that the opiates produce a predictable threshold-raising action with regard to pain. Yet, it is common experience that, after opiates, the cat's behavior differs dramatically from that of man. Indeed, frenzy, rather than contentment, is a common feature in cats.

Cushny (5) mentions that, while a constant pain in a patient is alleviated by morphine, a suddenly introduced painful stimulus causes the patient to be aware of the new pain as though he had had no morphine. This discrepancy may be understood as follows: As a result of the morphine his changed emotional state would make him react indifferently to his constant pain. Yet, since morphine may not appreciably raise the pain threshold in a subject having prolonged pain, he might be keenly aware of any new painful stimulus.

Opiates as therapeutic agents. The therapeutic action of opiates may be considered under three categories: (*1*) the threshold-raising action; (*2*) the property of dissociating pain perception from reaction in such a way as to free pain of its implications; and (*3*) the property of inducing lethargy and sleep.

1. *Threshold-raising action.* When opiates are administered 90 minutes before the introduction of pain, their threshold-raising action is considerable and is probably an important part of their therapeutic usefulness. This is exemplified by the analgesic effect of morphine when administered before surgical operative procedures. When thus given, the "saturation" quantity of codeine phosphate is 60 mgm. and optimal pain threshold-raising effects with morphine sulphate are attained with 15 to 30 mgm. After larger quantities, vomiting and other distressing symptoms often result. During severe pain of long duration, the threshold-raising action of the opiates is reduced and may even be obliterated. Under these circumstances their therapeutic value is chiefly through effects on the reaction pattern to pain and sleep-inducing effects.

2. *Alteration of the pattern of reaction to pain.* A major function of the opiates is to bring about a change in the pattern of reaction to pain so that, although pain is perceived, it does not bring forth the usual responses, such as anxiety, fear, panic, withdrawal, and flight. For example, in instances of intermittent pain, as during parturition, there is afforded opportunity for relaxation and even sleep between labor pains. With continuous pain, the individual becomes more capable of tolerating the experience when it is freed of its implications.

Consideration of the therapeutically useful quantity and duration of action of the opiates is relevant. It has been shown that the threshold-raising action of the opiates cannot be made to exceed well-defined limits regardless of the quantity administered. It has also been shown that the peak of the threshold-raising effect is reached, regardless of quantity administered, in approximately 90 minutes after administration. To what extent these values are relevant to the aforementioned psychological effects is important. But calibration of these qualities is less precise than threshold-raising action.

Many of the psychological effects pertaining to the pattern of reaction to pain did not have the same time-action curves as did the pain threshold. As described above, therapeutically important psychobiological effects, other than those of threshold-raising action, were attained within 20 minutes of administration and long outlasted the threshold-raising action of the opiates.

It is a common impression derived from bedside experience that the therapeutic effectiveness of a given quantity of opiate can be determined within

30 minutes of the time of administration, and if the patient is by that time still uncomfortable he needs more opiate to achieve a satisfactory therapeutic result. The validity of this position cannot at present be challenged. The question may be raised, however, as to whether the psychobiological effects are maximal at such time, or simply pronounced. A doubt may also be expressed as to whether amounts greater than "saturation" raise therapeutic effectiveness by inducing more satisfactory effects upon the reaction pattern of pain.

Attention may be focussed again upon the fact that pain is a potent antagonist of opiate action. This has been clearly demonstrated as regards threshold-raising effect, and less precisely, though definitely, as regards intensity and duration of other psychobiological effects. It is likely, in an analogous way, that pain antagonizes the respiratory depressant action of the opiates. Therefore, if with pain of high intensity larger than the aforementioned quantities of opiate should be used for therapeutic purposes, and if the pain should spontaneously stop, the antagonistic effect of pain upon this respiratory depressant action of the opiates will be as suddenly diminished, and serious toxic sequelae may follow.

3. *Induction of lethargy and sleep.* Lethargy and defects in mentation are not the essential components of the action of morphine in relieving anxiety, for with barbiturates extreme lethargy and difficulty in mentation may occur with little diminution in anxiety. Thus, evipal has been observed to induce with lethargy an unpleasant rush of thoughts with reiteration of unresolved personal problems and secondarily induced anxiety not unlike that of delirium. The subject may feel frightened, bewildered and uncertain. Furthermore, lethargy and mentation difficulties may accentuate anxiety, possibly because the subject feels inadequate to deal with his problems. However, when combined with freedom from anxiety, lethargy by inducing immobility or sleep may be a therapeutic asset. In preliminary experiments, sleep has raised the pain threshold 50 per cent.

SUMMARY AND CONCLUSIONS

1. Quantitative measurements of the pain threshold were made by irradiating 3.5 square centimeters of skin surface for 3 seconds. The intensity of radiation, which barely evoked pain, was denoted as the pain threshold. The threshold-raising action of various opium derivatives was then ascertained in terms of the normal threshold. Morphine sulphate in quantities from 0.1 mgm. to 30 mgm., and codeine phosphate in quantities from 15 mgm. to 240 mgm. were thus assayed.

2. The minimum effective quantity of morphine sulphate was 0.5 mgm. The "saturation" quantity, or the smallest amount with which the highest threshold-raising effect was attained, was approximately 30 mgm. The "saturation" quantity of codeine phosphate was 60 mgm. The "saturation" level for morphine sulphate, or the highest threshold-raising effect of which the drug was capable, was 100 per cent above the control threshold. The "saturation" level for codeine was 50 per cent above the control threshold.

3. The maximum threshold-raising effect for quantities of morphine sulphate in 0.5 mgm. to 15 mgm. was reached at approximately the same time; that is, about 90 minutes after administration. Other opiates tested took approximately the same time.

4. The time-action curve of threshold-raising effect for morphine sulphate revealed that essential elimination increased at a constant rate with quantities up to 15 mgm. However, with larger quantities of the agent, there was acceleration of the essential elimination rate so that duration of effect with 15 or 30 mgm. of morphine differed but slightly. The time-action curve for codeine phosphate revealed essential elimination at a constant rate up to 60 mgm. With larger amounts there was acceleration of essential elimination.

5. The threshold-raising action of dihydromorphinone hydrochloride ("Dilaudid") (3 mgm.), methyldihydromorphinone ("Metopon") (6.6 mgm.), and pantopium hydrochloride ("Pantopon") (20 mgm.), was measured. The above amounts of the first two agents had time-action curves comparable to that obtained with 30 mgm. of morphine. On this basis, pantopium (20 mgm.) was equivalent to approximately 8 mgm. of morphine sulphate.

6. The threshold-raising action of opium derivatives, as well as other observable effects, was reduced or obliterated by pain. A uniform pain

stimulus had a greater neutralizing effect on the threshold-raising action of these agents when the pain occurred just before or during the first 90 minutes after administration of the opiate. Thereafter, pain had less effect on the threshold-raising action. In other words, if pain preceded or occurred early in the course of the action of the opiate, it reduced or neutralized the threshold-raising effect of these agents.

7. This antagonism between pain and the threshold-raising action of opiates was simulated by the administration of a sympathomimetic agent (epinephrine) before the opiate was administered. It is possible that the heightened sympathetic activity, which is secondary to pain, is a factor in the above described antagonism.

8. In normal subjects the outstanding psychological effects of morphine were: freedom from anxiety, feelings of contentment and relaxation, apathy, difficulties in mentation, lethargy and sleep. Of especial significance were the emotional states referred to as freedom from anxiety and feelings of contentment. While in these states the subjects perceived pain, but the usual reaction pattern to pain was altered. It is suggested that the presence of an opiate accentuates the ability to dissociate pain perception from the pattern of pain reaction. It is postulated that much of the therapeutic effectiveness of opiates in the management of pain is based on their ability to alter the usual withdrawal fight-flight-anxiety reaction pattern of pain to one of freedom from anxiety, indifference, or apathy.

9. The therapeutic effectiveness of the opiates is dependent mainly on three properties: (*1*) threshold-raising action; (*2*) the dissociation of pain perception from the usual reaction to pain; and (*3*) the induction of lethargy and sleep.

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