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THE EFFECT OF ANALGESIC DRUGS ON THE SENSATION OF THERMAL PAIN IN MAN

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An analgesic drug would be expected to be capable of diminishing the perception of a suitable painful stimulus in the normal human subject. In past years, much effort has been expended in this direction using a variety of stimuli applied to the surface of the body—mechanical, electrical, and thermal. In all, the principle has been to apply to the subject an increasing measurable stimulus of relatively short duration until the sense of pain is recognizable. This stimulus is called the pain threshold. After the administration of a drug, the need to increase the intensity of the stimulus in order to elicit the same intensity of pain is considered to indicate an analgesic effect. The intensity and duration of such effects are studied at various dose levels.

An examination of previous publications reveals a natural tendency to base conclusions on too few subjects, sometimes on the authors only. The morphine group of analgesics and their synthetic substitutes are notorious for their side-effects which might influence the perception of a noxious stimulus so that an adequate number of subjects must be tested and the stimulus used must easily be recognized. No method so far evolved has withstood critical examination by other investigators. The failure of experimental methods may well be related to the application of stimuli of short duration to the body surface, whereas clinical pain is so often related to deep structures and is more sustained. In the absence of a satisfactory method of assessing analgesic potency in man, the relative efficacy of these compounds is usually related to morphine on the basis of animal tests of questionable validity.

The present paper is concerned with the effect of analgesics on the thermal pain sense in man. In theory, thermal stimuli possess the great advantage that the quantity or intensity of stimulus applied can be measured with accuracy. In practice, exact measurement of a thermal stimulus applied to the skin is difficult. Whilst the quantity of heat supplied to a given area of skin can be estimated with accuracy, a fraction of this, of unknown and varying magnitude, is dissipated by the blood supply to the area and in evaporating sweat, instead of being used to raise the temperature of the nerve endings. Thus, whilst control experiments carried out in surroundings of uniform temperature and humidity on a given skin site of constant initial temperature (e.g. the centre forehead) may give uniform threshold determinations (Hardy, Wolff, and Goodell, 1940a ; Schumacher, Goodell, Hardy, and Wolff, 1940), the marked autonomic effects of analgesic drugs (flushing, pallor, sweating) are liable to produce alterations in the thermal capacity of the skin of unknown and irregular magnitude (*vide infra*).

Hardy, Wolff, and Goodell (1940a) used an apparatus with which they and others have made extensive studies on the cutaneous sensations of heat and heat-pain (Oppel and Hardy, 1937 ; Hardy, Wolff, and Goodell, 1940, 1943a, 1943b, 1945 ; Schumacher, 1943 ; Wolff, 1947). For their studies on analgesic drugs these authors measured the quantity of heat required to produce a painful sensation on the centre of the forehead using a constant exposure to the stimulus of three seconds duration. After administration of a drug, threshold estimations were carried out at intervals of ten minutes and any increase in the quantity of heat required to elicit pain was regarded as an analgesic effect. This method suffers from the disadvantages referred to above. For example, Bigelow and Harrison (1944), studying the analgesic effect of intravenous procaine, noted that analgesia varied according to the subjective and objective disturbances produced by the drug. Whilst the results published by Hardy, Wolff, and Goodell (1940b) and others appeared to be very satisfactory, various workers have either recorded their inability to use the method (Dodds, Lawson, Simpson, and Williams, 1945 ; Thorp, 1946) or obtained results varying considerably from those of these authors (Christensen and Gross, 1948).

In the work here described, the skin contact temperature was measured during the application of a thermal stimulus. Temperature measurement is a more reliable method of estimating the intensity of a thermal stimulus and the results can be directly compared with those obtained in the rat by a similar technique (Jackson, 1952). Several modifications of the radiant heat technique have been applied to rats (Andrews and Workman, 1941 ; Smith and D'Amour, 1941 ; Ercoli and Lewis, 1945 ; Thorp, 1946), but the results are not directly comparable with those obtained in the human subject.

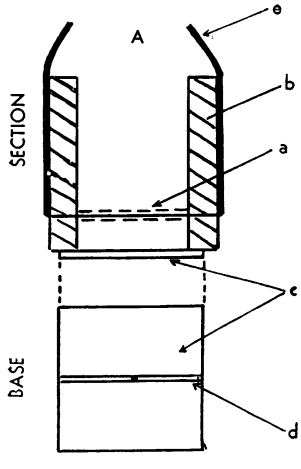
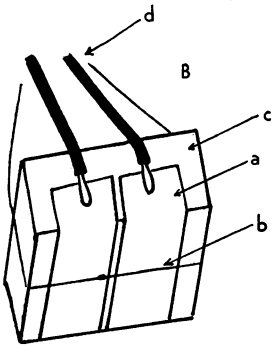


FIG. 1.—Apparatus for applying a known thermal stimulus to the skin. (A) *a*, heating element wound on a mica plate. *b*, asbestos mount. *c*, copper plate. *d*, thermocouple. *e*, heater and thermocouple leads. (B) *a*, heater element. *b*, thermocouple. *c*, mount. *d*, heater and thermocouple leads.



METHODS AND MATERIALS

Two forms of contact heater were used (A and B, Fig. 1). The first consists of a smooth, square copper plate (3 cm. square, 1 mm. thick) heated by radiation from a small electrically heated Nichrom element placed a few millimetres distant. The copper plate ensures that the heating of the skin in contact with it is uniform. Interposed between the copper plate and skin is a fine copper-constantan thermocouple connected to a sensitive recording galvano-

meter. This stimulus involves a reaction time of about 25 to 30 seconds using a current of 2 ampères at 10 volts provided by a transformer from the mains supply. A few minutes are required for cooling so that single threshold estimations can be performed at intervals of about five minutes.

The second type of heater used (B, Fig. 1) consists of two strips of uniform Nichrom resistance tape (0.006 inch thick) connected in series and arranged side by side so as to form a heating surface of 2.5 sq. cm. For use it is strapped to the skin and an alternating current of 5 to 6 amperes at 10 volts is required to produce a suitable rate of heating. The skin contact temperature is again measured by a thermocouple of low thermal capacity running transversely across the heater. The thermal capacity of the heater is minimal, for immediately the current is discontinued the temperature ceases to rise and cooling is rapid. Stimuli may therefore be applied in rapid sequence when necessary.

It is obviously most important to ensure uniformity of heating and an accurate response of the thermocouple. The transverse position of the latter was chosen to minimize heat loss along the wires.

The 23 subjects used in these experiments were of both sexes, mainly of the student age group; a few were of middle age. They were recumbent during the experimental period. Control determinations were first made until the temperature of pain perception was constantly recognized. The subject expressed vocal appreciation of the end-point and an observer noted the galvanometer reading. Various sites of the body were chosen for different experiments, but for prolonged tests the lateral aspect of the calf was commonly used. In earlier experiments isolated threshold estimations were made at intervals of about ten minutes, as was the practice of previous workers using radiant heat (Hardy, Wolff and Goodell, 1940a), but later more frequent stimuli were applied.

Drugs were given subcutaneously, intramuscularly, or intravenously; some subjects took part in only one experiment, whilst others submitted to several tests at varying dose levels or had different drugs. Nitrous oxide inhalations were made from a Douglas bag containing gas mixtures of known composition, analysed by the excellent method described by Chaney and Lombard (1932). The gas mixture was administered through a nasal inhaler.

There are various local and general factors which might influence the pain threshold level in any subject. The more important are psychological effects, the rate and frequency with which the stimulus is applied, the site of stimulation, and the initial skin temperature. These are referred to later.

RESULTS

In estimating the pain threshold it is of importance that the element of pain should be recognized as soon as possible—yet it has to be sufficiently sharp to be easily perceptible in spite of any peculiar sensations which might follow administration of a drug. The sensations produced by the heating elements used correspond closely with those described by Wolff and his collaborators (1940a)—a sense of warmth, replaced by increasing hotness and followed by a distinct throb of pain which is recorded as the threshold. Should heating be continued further, the sense of pain increases with surprising rapidity, and soon becomes intolerable to most subjects. The thermal threshold for pain has been investigated by other workers. Weber (1846) considered that the temperature required to produce pain was so high that, acting for a little time upon nerve, it limited conduction; he gave this temperature as 48.7° C. Lewis and Love (1926) included a study of thermal pain in their investigations of cutaneous sensations and reactions. They found the element of pain normally commenced at a surface temperature of 43° C. or a subcutaneous temperature of

38° C. and that these temperatures are close to those producing an injury flare. They maintained that 43° C. was intolerable to most skins under conditions of asphyxia which allowed the heat to penetrate, or 42° to 43° C. if the thermocouple was inserted into the skin. More recently, Lloyd-Smith and Mendelssohn (1948) determined the skin temperature exposed to radiant heat for 15 minutes which produced a pricking pain and recorded a temperature of 45° C. By means of the heater A (Fig. 1) the mean thresholds for a number of subjects of both sexes were calculated from single stimuli delivered at intervals of about ten minutes ; the results are presented in Table I. Some of these may also be seen in graphical form in Fig. 2. It was found

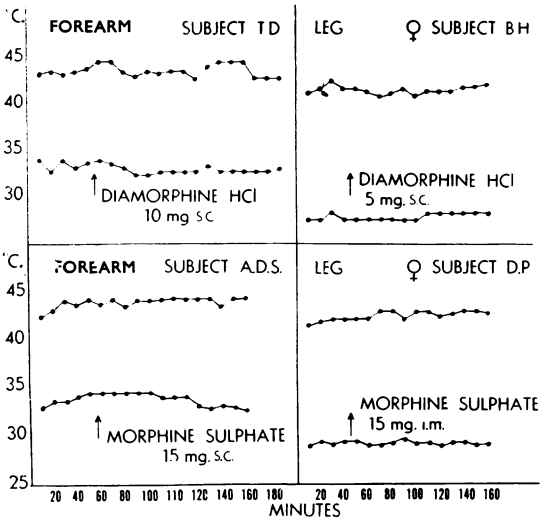


FIG. 2

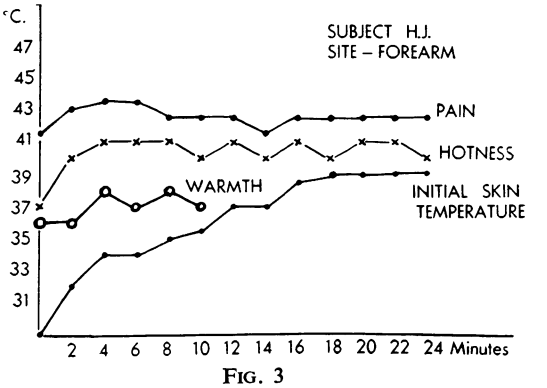


FIG. 3

FIG. 2.—Four examples of the failure of subcutaneous morphine and diamorphine to affect thermal pain perception. Single estimations of the threshold (the upper series of points in each graph) were made at intervals of about 10 min. from the initial skin temperatures indicated (lower points in each case). The first few points establish uniformity of the normal response before administration of the drug at the times indicated. No significant change in pain threshold occurred subsequently in these subjects or in any of a total of 15 individuals tested.

FIG. 3.—The effect of changes of initial skin temperature on the perception of thermal sensations. The temperature of the forearm was steadily increased by means of an electrically heated pad, and estimates of the sensations of warmth, hotness and pain made at intervals of 2 min. Although the initial skin temperature rose during the experiment by 10° there was no effect on the perception of thermal pain or the sensation of hotness. The onset of warmth was perceptible until the skin temperature reached the warmth threshold at about 37°.

that the initial temperature of the skin has little or no influence on the pain threshold with occasional stimuli. In the experiment summarized in Fig. 3, the temperature of the arm was slowly raised by means of an electrically heated pad whilst repeated estimates of the threshold were made ; the onset of the sensations of warmth and hotness was also noted. When the arm temperature reached 36° C. the sense of warmth was no longer perceptible, whereas the perception of hotness and pain remained at steady levels throughout. When stimuli are applied in quite rapid succession, e.g. one per minute, for considerable periods of time, the threshold tends

to be somewhat higher (compare Tables I and II). These periods of stimulation do not produce any noticeable damage beyond an erythema ; Lewis (1942) commented that the onset of pain occurred at a temperature at which tissue damage commenced

TABLE I

NORMAL THERMAL THRESHOLDS

Single stimuli at intervals of 10 min.

Subject	Site	Temperature °C.		Number of stimuli
		Initial	Mean threshold	
D.P. (f.)	Leg	30	41.5	8
E.B. (f.)	Leg	29	42.25	9
K.H. (f.)	Leg	29	41.25	14
M.B. (f.)	Leg	29	41.0	5
M.B. (f.)	Leg	29	43.0	5
J.A. (f.)	Leg	29	40.0	10
J.H. (m.)	Forehead	35	44.0	6
H.J. (m.)	Forehead	34	42.5	8
T.D. (m.)	Forehead	34	43.5	4
T.D. (m.)	Forehead	34	44.5	5
L.K. (m.)	Forehead	35	43.5	4
L.K. (m.)	Forehead	35	43.5	2
A.G. (m.)	Forehead	35	44.5	6
A.S. (m.)	Forehead	35	44.0	5
H.J. (m.)	Forehead	35	43.0	9
H.J. (m.)	Forehead	35	43.5	10
F.H. (m.)	Leg	30	41.25	6

TABLE II

NORMAL THERMAL THRESHOLD

Site: Arm and leg. Initial temp. 34.5. Stimulation: 1 per min.

Subject	No. of stimuli	Mean threshold (°C.)
H.J. (m.)	29	45.0
H.J. (m.)	19	45.0
H.J. (m.)	6	44.0
H.J. (m.)	12	46.5
H.J. (m.)	10	45.5
L.K. (m.)	19	45.0
A.H. (f.)	45	42.0
A.H. (f.)	27	43.5
L.K. (m.)	12	46.0
L.K. (m.)	4	45.5
S.D. (f.)	19	44.0
S.D. (f.)	7	44.0
S.D. (f.)	10	42.0
E.H. (f.)	14	43.5
J.L. (m.)	9	44.5
D.D. (m.)	10	43.0
G.W. (m.)	15	45.5
J.G. (f.)	20	45.0
F.H. (m.)	7	44.0
F.H. (m.)	4	45.5
A.P. (m.)	8	45.0

as manifest by flare production. In some subjects the threshold varied from day to day as much as 2° C., but remained constant during an experimental period. If the skin is damaged with an erythema dose of ultra-violet light, the threshold soon falls, even down to blood temperature, and recovers in the course of a few days (Fig. 4).

It became apparent that no significant change occurred in the thermal pain threshold in most subjects after therapeutic doses of analgesic drugs (Fig. 2) when single stimuli were applied at intervals of ten to fifteen minutes. The possibility that the stimulus used was too intense appeared unlikely in view of the observation that individuals recognizing a pain threshold two or three degrees lower than most were also unaffected by these doses of analgesic drugs and also that the sense of " hotness," when recorded, also remained unimpaired.

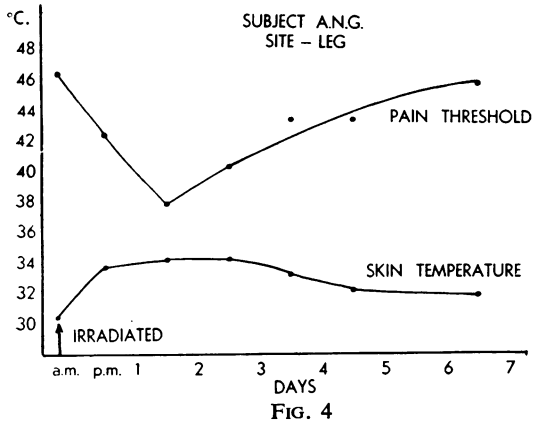


FIG. 4

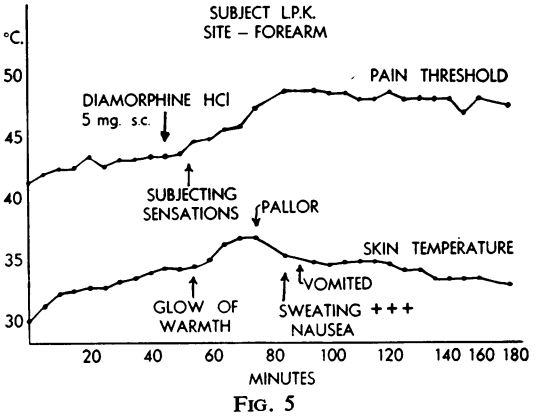


FIG. 5

FIG. 4.—This experiment illustrates the depression of thermal pain threshold (upper curve) almost down to blood temperature, which takes place after a small area of skin is given an erythema dose of ultra-violet light. A few days is required for restoration to normal levels. Note the associated rise in skin temperature due to the erythema.

FIG. 5.—An unusual response to the subcutaneous injection of diamorphine. This subject showed elevation of the thermal threshold (upper curve) associated with a severe vasomotor-type of reaction. The persistent elevation of the threshold is apparently due to damage to the skin which occurs at this temperature (48°).

Only one subject (L.P.K.) showed a progressive increase in threshold and that occurred after the administration of diamorphine for the first time (Fig. 5). Soon after the drug had been given, he showed a striking vasomotor reaction—intense pallor, severe sweating—and vomited once. The threshold rose to 48° C. and persisted at this level. After 140 minutes an adjacent site was heated and gave normal threshold readings, so that obviously the repeated stimulation to 48° C. had impaired the sensibility of the skin. In a repetition of this experiment a few weeks later, a similar but less intense reaction occurred, but there was no alteration in threshold.

In further attempts to demonstrate an effect of analgesics on pain threshold, stimuli were applied in rapid succession to see whether analgesic drugs produce some kind of fatigue phenomenon. In one series of experiments the initial heating to threshold was followed by three or four others in quick succession from a constant initial temperature and the mean value calculated. Intervals of about ten minutes

were allowed between each series of heatings (Fig. 6). Finally, stimuli were applied steadily at intervals of about one per minute from a constant initial temperature for prolonged periods of time (Fig. 7). In both these groups of experiments, morphine and diamorphine were administered intravenously. Three of the seven subjects who

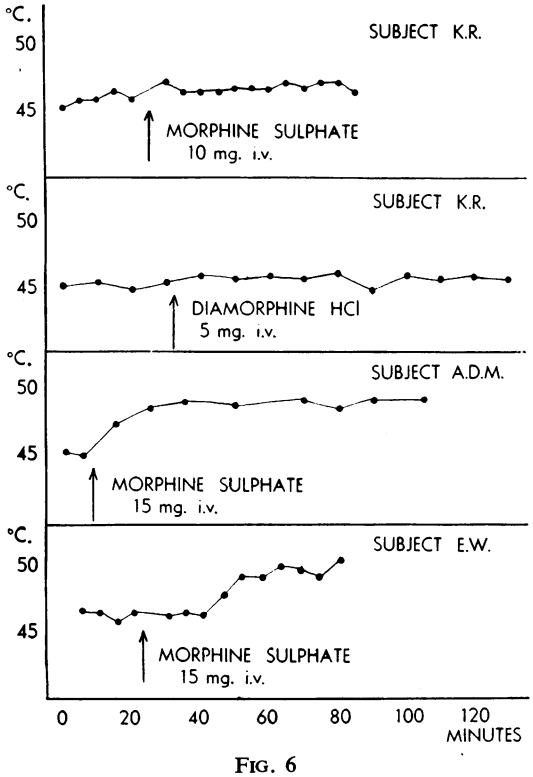


FIG. 6

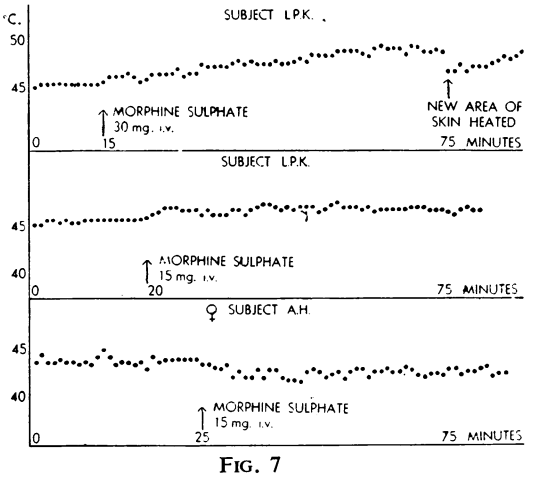


FIG. 7

FIG. 6.—The intravenous injection of morphine and diamorphine and the perception of thermal pain. Four examples are shown in which each point on the graphs represents the mean of at least three estimates of the thermal threshold made in rapid succession from an initial skin temperature of 35°. Marked elevation of threshold occurred in subjects A.D.M. and E.W. Subject K.R. maintained his normal threshold level throughout.

FIG. 7.—The perception of thermal pain after intravenous morphine. Estimates of the thermal threshold were made at intervals of 1 min. Subject L.P.K. showed a noticeable rise after a dose of 15 mg., whilst 30 mg. elevated the threshold to a level considered intolerable by normal individuals. On the other hand the threshold of A.H. (lowest graph) became lower after 15 mg. of the drug.

submitted to the experiments did show a progressive rise in threshold to relatively large doses of morphine. The maximum temperature reached was in the region 48° to 49° C. The duration of effect is unfortunately unknown, since successive heating to these levels damages the skin ; thus, stimulation of a fresh area of skin after an hour or so in each case gave normal readings.

The side-effects which accompanied the use of these drugs, especially the large intravenous doses, made further experiments on this scale unjustified.

The temperature of maximum tolerable thermal pain

Using a copper bar as heat reservoir, Lewis and Love (1926), with two subjects, recorded a surface temperature of 47° to 48° C. as intolerable for more than 5 seconds. These authors stated that if the skin temperature is raised gradually, a surface temperature of 51° to 52° C. may be borne, but related this to coincident damage impairing the sensation. In the present experiments, the heater was strapped in position, and, starting from a constant initial temperature of 37° C., estimations of the pain threshold were made, each being followed by continued heating until the subject found the pain intolerable. In the subjects tested (four in number), the maximum achieved was 48° to 49° C. Even after more than ten such heatings, the perception of pain in the heated area remained normal, although the area was obviously damaged and subsequently developed a blister (Fig. 8). The duration of each heating was about 15 seconds.

The effect of asphyxia on the perception of thermal pain

Using the radiant heat technique, Hardy, Wolff, and Goodell (1940a) maintained that occlusion of the circulation in the arm was followed by a progressive increase in the pain threshold of the hand to a maximum of about 30 per cent at the end of the 35-minute period of asphyxia. When the circulation was restored, the threshold rapidly returned to normal. With the same technique, Thorp (1946) found a peak of " analgesia " occurred after the pressure was released (50 per cent increase), the rise during the asphyxial period being about 30 per cent. Lewis (1942), however, had previously stated that production of a state of asphyxia in a limb lowered the perception of thermal pain on the skin of the limb, because arresting the circulation allowed heat to penetrate more easily ; a skin temperature of 42° to 43° C. was said to be intolerable under these circumstances. According to Lewis, therefore, a state of hyperalgesia rather than analgesia is produced. Fig. 9 illustrates the effect of asphyxia using thermal stimuli applied to the forearm in rapid sequence from a constant initial temperature. The threshold diminishes until a fairly steady value is reached about 2° lower than the control readings. After restoration of the circulation, there is a rapid and transient increase in threshold which corresponds to the period of severe " pins and needles " which naturally occurs at this time and makes the perception of the thermal stimulus difficult. On the basis of this typical experiment, together with Lewis's observation, it seems that the radiant heat technique in the studies referred to above can give misleading results.

The inhalation of nitrous oxide and thermal pain

The inhalation of even relatively small percentages (e.g. 20 to 30 per cent) of nitrous oxide produces well-marked subjective sensations and objective changes in the human subject. Marked analgesic effects are stated to occur with moderate percentages (45 to 50 per cent) in obstetrical cases. Seevers, Bennett, Pohle, and Reinardy (1937) studied the effect of nitrous oxide on the pain threshold to pin-prick as measured by the Frey hair technique. In the present experiments, it was expected that the thermal pain threshold would show progressive elevation until the subject became uncooperative but not unconscious. However, the threshold proved remarkably resistant to change, even in a number of subjects who had no previous

experience of inhaling volatile anaesthetics. About 70 per cent of nitrous oxide was required to cause any change and the maximum threshold observed prior to unconsciousness was again 48° to 49° C. (Fig. 10).

FIG. 8

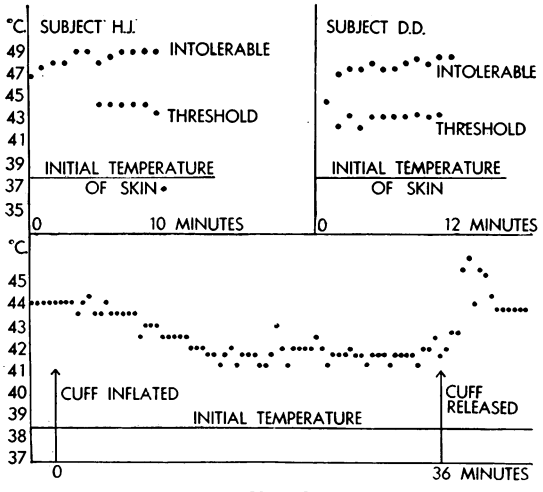


FIG. 9

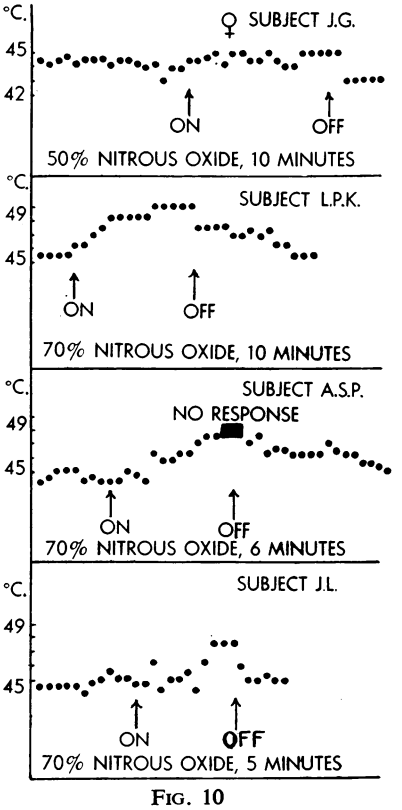


FIG. 10

FIG. 8.—The maximum tolerance for thermal pain. Successive heatings of the skin were made to the level of intolerability (upper points) from an initial temperature of 38°. Although the skin was obviously damaged at the conclusion of the experiments (about 10 min. in each instance) and subsequently blistered, the perception of thermal pain remained unimpaired (lower points).

FIG. 9.—The effect of asphyxia on the perception of thermal pain. The thermal threshold was estimated on the forearm at half-min. intervals, and the circulation occluded by means of a cuff. Note the progressive fall in pain threshold (over 2°) which followed. When the circulation was restored after 36 min. the threshold rises temporarily but soon returns to normal.

FIG. 10—Examples of the effect of nitrous oxide on thermal pain perception. The points represent the pain thresholds obtained by successive skin heatings from an initial skin temperature of 38°. In general, 70 per cent of the gas was required to elevate the threshold significantly without producing unconsciousness. The maximum threshold registered by any subject (10 tested) was about 49°.

DISCUSSION

The results presented above show that the temperature at which a thermal stimulus is first perceived by the human subject is unaffected by therapeutic doses of morphine or diamorphine. In addition, it has proved surprisingly difficult to elevate this threshold temperature either by the induction of asphyxia in the area

stimulated or by inhalation of nitrous oxide. Intravenous injection of larger doses of morphine or diamorphine has produced rather ill-defined elevation of the thermal threshold by 3 or 4° C. in three of seven subjects tested ; damage to the skin soon occurs at these higher temperatures. It appears that the maximum rise in temperature which may occur is to the 48°–49° C. level. This limitation is probably imposed by the factors of maximal stimulation of nerve endings and concurrent damage. As a result of this relatively small temperature rise, the large dose of opiate required, the uncertainty of the response in different subjects, and the unpleasant side-effects of the drugs (vomiting especially), the use of thermal stimulation for the assessment of the analgesic potency of drugs is impracticable.

The results of some previous workers using radiant heat as the stimulus, in which smooth and well-defined " analgesic " effects were obtained with therapeutic doses of morphine and related compounds, must have some other interpretation. It is established that widely varying results have been obtained by different groups of workers using such a technique. How then may these findings be reconciled with the readiness with which thermal pain perception is apparently abolished in the rat, as judged by the tail reaction ?

In man, thermal pain is perceived in the region of 43° C., using occasional stimuli ; in the rat under similar circumstances, the tail reaction occurs at about 38° to 40° C. (Jackson, 1952). This latter zone of temperature corresponds roughly with the sense of hotness in man, which the animal is likely to interpret as noxious. Doses of analgesic drugs, not far removed from those used in man on a weight basis, readily elevate the reaction temperature in rats to 48° C. A tail response above this level is rarely obtained and skin damage will occur ; " analgesia " is thus complete. This temperature is similar to the maximum threshold (48° to 49° C.) observed in human subjects treated with analgesics or nitrous oxide and to the temperature at which a thermal stimulus becomes intolerable. It therefore seems reasonable to suppose that thermal analgesic tests in rats do in fact measure " analgesia." The lack of a similar effect on threshold in man could be a question of magnitude of dose.

Summary

1. Temperature measurement is claimed to be the most satisfactory method of determining the intensity of a thermal stimulus applied to the skin.

2. On this basis, the threshold to thermal pain in man and the tail response in the rat are similar.

3. The thermal threshold in man is very resistant to elevation. In most subjects tested, therapeutic doses of analgesic drugs had no significant effect. Asphyxia for 40 minutes in a limb lowers the threshold temperature.

4. Relatively large intravenous doses of morphine and diamorphine raised the threshold by as much as four degrees centigrade (to 48° to 49° C.) in a minority of subjects. This increase appears to be the maximum attainable in man, and corresponds with the maximum temperature of response observed in the rat (48° C.).

5. The magnitude of the dose required to elevate the threshold, the small change which may occur, and the uncertainty of the response in different subjects imply that in man thermal stimulation of the skin is an unsuitable method for assessing the analgesic potency of drugs.

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