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Chapter 38

Narcotics and Analgesics

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I. Introduction

In its broadest sense the alleviation of pain is one of the most important goals of scientists. Among natural products there is none which performs this function as surely and as dramatically as does morphine. Unfortunately morphine elicits other reactions, many of them undesirable ones, and

it is therefore little wonder that it has been subjected to an investigational scrutiny unequalled in science.

In 1943 the United States Public Health Service published the second volume of *The Pharmacology of the Opium Alkaloids* (1), the first volume having appeared in 1941. The volumes contain a very complete bibliography (estimated by Krueger as 99 %) of the literature on the pharmacology of the opium alkaloids through 1936. The subject matter of the body of the papers examined, as well as the key words of the titles, is included in an index of the literature. By the end of 1938 some 9069 references had been collected, and during the preparation of the manuscript 105 additional papers were read, examined, and indexed. While the manuscript was in press 7 additional papers were found for the period prior to 1937, and for the years 1937, 1938, 1939, 1940, 1941, and 1942, respectively, 33, 110, 150, 136, 129, and 44 references, collected while the manuscript was in press, were included in the second volume but they were not used for the text nor were they indexed. The text of *The Pharmacology of the Opium Alkaloids* contained a good summary of the pharmacological literature through 1937 and, though not so completely, also for 1938 and 1939. For some topics the review was critical and analytical; for other topics only a summary of the information was assembled.

Another summary with special reference to the chemical structure of opium derivatives and allied synthetic substances and their pharmacodynamic action is supplement No. 138 to the Public Health Reports of the U.S. Public Health Service entitled *Studies on Drug Addiction* and published in 1938 (2). Synthetic analgesics have been considered subsequently in many reviews. Extensively consulted in the preparation of this article were the reviews by Fellows and Ullyot (3), Lee (4), Wikler (5), Isbell and Fraser (6), Beckett (7), Schaumann (8), and Schoen (9). This review will mainly be concerned with analgesia, addiction, and fate, of morphine and related analgesics.

II. General Pharmacology of Morphine

The administration of morphine is followed by a series of complex events. Analgesia, euphoria, addiction, and respiratory depression are stressed in the literature, but if morphine had only its effect on carbohydrate metabolism it would rank with insulin and phloridzin in interest; if it had only its effect on smooth muscle it would rank with pilocarpine and physostigmine; and if it had only its effect on gastric secretion and salivation it would rank with histamine. But consideration of some effects is lost in the importance of analgesia and only possible counter indications to its use as an analgesic remain continuously on the experimental horizon.

The majority of the effects seen in man and other animals after the ad-

ministration of morphine may roughly be divided into two groups: effects dependent upon the central nervous system and effects dependent upon smooth muscle. The central nervous system and smooth muscle alterations are in part due to the presence of morphine and its metabolites, in part to alterations in the concentrations of hormones and tissue metabolites induced by the action of morphine, and in part to interactions between smooth muscle and the central nervous system, especially the sympathetic and parasympathetic components. Either the smooth muscle effects or the central nervous system effects may be in the direction of increased or of decreased activity. The central nervous system effects lead to a mixture of depression and stimulation of voluntary muscular activity. Stimulation may be so great as to cause convulsions with subsequent death.

In man the main events after morphine are a quieting effect with a tendency to sleep, a sense of well-being, and a decreased attention to the internal and external stimuli which give rise to discomfort and disagreeable sensations such as cough, fatigue, hunger, and pain. With sufficient morphine the depression deepens to unconsciousness and may lead to death. Increases in reflexes are rare and convulsions exceptional. However, convulsions are somewhat more easily obtained in children with codeine. With clinical doses of 15–30 mg. of morphine the sense of well-being or euphoria may involve dreams, usually of a pleasant nature, and for a few individuals, wild fancy through scenes of rapture and splendor. Vomiting, dizziness, loquaciousness, and vivacity are frequent. Less attention is paid to pain if present and the pain often disappears (1). Kolb and DuMez (10) indicated that most individuals experienced a relief of anxiety and pain from the administration of morphine but that the pleasure of being raised above the usual emotional plane develops mainly in the emotionally unstable, the psycopaths, or the neurotics. However, David (11) indicates that euphoria appears in about one-third of the individuals given morphine. Sometimes, more frequently in women than in men, morphine leads to excitement and even to delirium (1).

1. Sensations

The clinical importance of morphine depends upon its interference with the perception and interpretation of pain. While the mechanism may not be clear, there is no doubt about the effectiveness of morphine in producing relief from pain. It is important that morphine does not produce equally clear cut interference with other sensations. A cautious writer should interpose the comment that this may be due to the fact that the investigators have not been many nor have the investigations always been extensive.

Only minor disturbances in the sense of smell could be detected by

Fröhlich (12). After morphine administration some errors in odor identification were made, but the errors were least with disagreeable odors such as garlic, asafetida, and carbon disulfide. All substances seemed to be at a distance even when placed under the nose. Later Wikler, Wolff, and Goodell (5) found that morphine did not elevate olfactory thresholds.

Visual acuity was not altered in normal healthy human subjects by 10 mg. of morphine. The fields of vision for white and blue remained normal, but those for red and green were reduced (Macht and Macht, 13). However, visual thresholds were elevated to about ten times their original value by the administration of morphine to post-addicts (formerly addicts but now undergoing rehabilitation). The pupillary constriction produced by the morphine may have contributed to the elevation of the visual thresholds (Andrews, 14).

Thresholds of hearing in healthy human subjects for tones with vibration frequencies from 128 to 11,584 were decreased by 10 mg. of morphine. The decrease in acuity of hearing ranged from 5 to 20 decibels for various tones, the responses to higher frequencies being more affected (Macht and Macht, 15); but Wikler *et al.* (5) reported that morphine did not alter thresholds of perception for hearing in man.

Hilsmann (16) found no effect on two-point tactile discrimination, while Kremer (17) recorded a definite increase in the minimal distance for two-point discrimination throughout the surface of the body after 10–15 mg. of morphine was administered subcutaneously. David (11) reported recently that tactile discrimination was decreased in 6 of 10 subjects with 10 mg. (0.14 mg./kg.) and was uniformly decreased in all subjects by 15 mg. (0.22 mg./kg.). Mullin and Luckhardt (18, 19) claimed that tactile sensitivity was not appreciably affected by doses of morphine (35–30 mg.) which reduced sensitivity to pain. Further, according to Wikler *et al.* (5), the administration of morphine did not alter thresholds of perception for touch, vibration, two-point discrimination, or hearing in man, and hence morphine specifically alters pain thresholds. Wikler felt that this inference was open to question because of the variable effects of analgesics on pain as reported by different investigators (5).

Rhode (20) reported an immediate increase in the threshold for pain and temperature after 15 mg. of morphine subcutaneously, but touch and pressure sensations were only slightly decreased. Grünthal and Hoefer (21) noted no definite effect on cold and warm sensations after 10 mg. of morphine, but pain and pressure sensations were definitely diminished.

2. Learning and Association

The dreaming and relief of anxiety after morphine suggest that learning and association patterns may be altered. That this is true is indicated by

the response of post-addicts to Rorschach patterns and by the alteration of conditioned reflexes in dogs. Morphine (34 mg.) altered the response of post-addicts to Rorschach patterns in that under morphine the post-addicts noted more details, more rare details were described, and the number of interpretations of the Rorschach designs as representing human movements were increased. Neurotic signs were reduced and signs of intellectual control, organizational energy, and originality were not affected. The personality of the post-addicts changed in the direction of increased phantasy living. Morphine also reduced the differences in responses between non-disturbing and disturbing (drug, sex, crime, etc.) word stimuli (5).

Morphine exerted similar effects on the learning of dogs. In basically neurotic dogs, morphine abolished whatever conditional responses they had learned and induced a neurotic response. In a dog that had been able to differentiate six tones in a narrow range and thus might be termed *stable*, morphine, in the early period of training, impaired the ability to differentiate between tones; but in the late period of training when the conditioned reflex had been well developed, morphine did not impair the differentiation. In this dog excitement and a failure to distinguish between tones developed when efforts were made at having the dog unlearn the conditional response. Morphine decreased the intensity of the excitement and restored the ability to differentiate between positive (requiring a response) and negative signals (not requiring a response).

The variable effects of morphine on association and learning in both man and dog can be correlated to some extent with those groups of characteristics which are commonly referred to as personality (5).

3. Respiration

The effects of a drug upon circulation and respiration are of prime importance in determining their safety in clinical use. If one follows published opinion one must come to the conclusion that morphine depresses the respiratory center. If one analyzes the published data, it is difficult to substantiate such a decision. Extensive data on the respiratory effects of morphine in the rabbit, dog, and cat are available and have been discussed in detail elsewhere (1). The concept of a depression of the respiratory center by morphine was initiated by the *ex cathedra* statement of van Bezold (22). Fluorens' paper (23) on the location of the vital node or the first motor point of the respiratory mechanism had been published a few years earlier, and this probably served to focus attention on the respiratory center and led to the very logical explanation of decreased respiratory movements on the basis that morphine depressed the respiratory center.

There are four prime observations which lend support to the hypothesis that morphine makes the respiratory neurons *less active* and *less capable of*

activity than normally: (1) The minute volume of respiration is reduced by morphine and the alveolar carbon dioxide tension is increased. (2) The administration of carbon dioxide leads to a greater absolute and a greater relative increase in respiratory minute volume in the normal than in the morphinized animal. (3) Morphine prolongs the apnea obtained on artificial ventilation. (4) There is a development of periodic respiration under some conditions of morphinization.

However, there are some facts which are difficult to explain on the basis of a depressed respiratory center, and there are other facts which suggest a different explanation. In the first place the decreased oxygen consumption after morphine and the quieting effect indicate a decreased respiratory minute volume requirement. But the decrease in respiratory minute volume can be interpreted as greater than the decrease for which these two components might account. Yet the subcutaneous administration of 5 mg. of morphine cuts the normal minute volume of the rabbit in half, while the oxygen content of the expired air is not reduced below 17.8%.

The second fact which suggests that the respiratory center is not depressed is the consideration that, if a dose of morphine is given and a marked depression of respiratory minute volume is obtained, further doses of morphine lead to a respiratory stimulation. It is difficult to imagine how the capabilities of a cell can be depressed almost to zero, and then be resuscitated by still more of the depressing agent. Further, the administration of morphine leads to increased respiratory minute volume in the midbrain rabbit, that is, in a rabbit whose cerebral lobes and thalamus have been removed but whose medulla and respiratory center in the medulla are still reasonably intact (1).

Dressler (24) showed that the greater effectiveness of carbon dioxide in increasing respiratory minute volume in normal rabbits did not hold for high concentrations of carbon dioxide. The relative increase in minute volume was greater in the morphinized animal with 10% and 15% carbon dioxide; the relative increase in respiratory frequency was greater with 2.5%, 4.5%, 10%, and 15% carbon dioxide in the morphinized than in the normal animal; and, with 15% carbon dioxide, tidal volume showed a relatively greater increase in the morphinized than in the control rabbit. Somewhat similar is the evidence of Yosomiya (25) that the maximum respiratory rate during progressive exposure to low oxygen occurs at 14% oxygen in the morphinized animal and at 6% in the normal animal. It would seem that the morphinized center responds to low oxygen much earlier and more extensively than does the normal center.

The data on the movement of carbon dioxide are also very difficult to explain on the basis of depressed respiratory neurons. If carbon dioxide tension in the lungs is increasing due to a lower ventilation level brought

about by a depressed respiratory center, there is a definite limit to the volume of carbon dioxide that would be retained by the blood and tissues. A comparison of the data of Wright and Barbour (26) and of Fubini (27) indicates a retention of about 15 vol.% of carbon dioxide for the whole rabbit, while the increase in alveolar carbon dioxide would account for an increase of only 3 vol.% (1).

A much better basis than depression of the respiratory center for the explanation of the carbon dioxide retention is the increase in alkaline reserve (1). If one assumes that the body attempts to maintain a constant pH and that the body is still partially successful in this attempt after the administration of morphine, an increase in base must lead to a retention of carbon dioxide to neutralize the base and a further retention to keep the acid-base ratio constant.

If carbon dioxide were piled up only because of decreased ventilation, blood and body acidity should have increased. But Gauss (28) found an alkaline change of 0.2 pH and Becka (29) of 0.49 pH. A depressed respiratory center demands changes in an acid direction. Thus the evidence indicates that the neurons of the respiratory center are not incapacitated or inactivated by morphine but can and do perform their tasks under certain conditions, and that a depression of the respiratory center does not adequately explain all the important pertinent respiratory data. The neurons are *less active* and their activity may be inhibited but they are still *capable of extensive activity.*

It remains to be seen if the evidence in favor of depressed neurons need necessarily be interpreted in that light. The reduction of respiratory minute volume and the increase in alveolar carbon dioxide may be explained on the basis of a decreased oxygen consumption and of an increased alkaline reserve. The greater increase in respiratory minute volume by low concentrations of carbon dioxide in the inspired air in normal animals can also be explained by the fact that a 1% increase in carbon dioxide concentration in the inspired air does not increase alveolar carbon dioxide tension to the same relative or absolute extent in the normal and morphinized animals.

The third line of evidence in favor of a depressed respiratory center may only mean that the same volume of hyperventilation will remove more carbon dioxide from the morphinized animals. Thus, one would expect a greater duration of the apnea after hyperventilation in the morphinized animal until the requisite amount of carbon dioxide has reaccumulated.

This leaves only periodic respiration. At present this is the main and only support for the hypothesis of a depression of the respiratory center by morphine. Periodic respiration indicates a definite interference with the activity of the respiratory neurons. It may be that periodic respiration will force a retention of the center depression theory, but periodic respira-

tion may also reflect periodic changes in the pattern of impulses playing on the respiratory center. Of prime importance is the fact that periodic respiration develops only after large doses of morphine.

In addition to the retention of carbon dioxide and the increased alkaline reserve, the secretion of an alkaline urine also indicates an alkaline phase after morphine (1). The secretion of HCl into the stomach with the pyloric sphincter closed offers a possible explanation of the alkaline phase. The total secretion of HCl obtained from a gastric pouch, in the experiments of Riegel (30) on dogs, with 5 mg. of morphine per kilogram, amounts to approximately 0.6 vol. % of carbon dioxide if calculated for the whole animal. Presumably the additional HCl secreted into the stomach proper and isolated from the body through the closure of the pyloric sphincter would be able to account for a much greater alteration of the alkaline reserve of the body. In an experiment of Hirsch, sufficient HCl was separated to account for a change of 1.8 vol. % in body alkaline reserve if the changes were distributed throughout the body or of 18 vol. % if confined to the blood, and this separation occurred in a 45-min. period just subsequent to the administration of 8 mg. of morphine. Additional amounts of HCl were separated later. In another experiment of Hirsch (31), the HCl separated into the stomach over a 2-hr. period was equivalent to 3.2 vol. % of carbon dioxide on the total weight basis and 30 vol. % if confined to the blood (1).

The time relation between the onset of gastric secretion and the increase in blood alkaline reserve is not clear. It is possible that the secretion of HCl into the stomach may account for the changes in alkaline reserve. At any rate an extensive series of experiments must be undertaken to analyze the possible interrelation between effects on respiration, alkaline reserve, and gastric acidity.

The depression of respiratory activity after morphine is the resultant of several factors (1). Among them may be a depression of the irritability of the respiratory center. Our position is that a much more rigid analysis of the facts available and the accumulation of a great deal more information is required before one can unconditionally accept the concept as true. In the majority of the data available at best we can make a comparison between the approximate steady states obtaining before and at some given time after the administration of the morphine. In order to attempt an adequate explanation of the respiratory effects of morphine, there is necessary a group of experiments studying the time course of numerous factors concerned in the chemical regulation of respiration (1). A series of experiments such as those developed in the laboratory of Gesell (32) would go far to provide a satisfactory background for the analysis of the complex respiratory phenomena obtained after morphine.

Although the function of respiration is more amenable to quantitative

study than any other, little quantitative information on the morphine problem has been gathered with man as the subject (1). Time and again reference is made to a slow respiratory rate after the administration of morphine, but seldom are sufficiently comparable control data available so that the magnitude of the drug action may be evaluated. Presumably this may be due to the fact that the respiratory rate was noted but seldom recorded unless obtrusively low and then if the patient subsequently recovered there was no need to determine the normal rate. Thus it is that many of the studies, particularly the early ones, on the respiratory effect of morphine in man are concerned primarily with the relation of respiratory depression and acute fatal morphine intoxication. The exigencies demanded, where a fatal outcome impends, preclude the possibility of more than descriptive observations.

In man the respiratory factors are usually not markedly changed by morphine. In resting healthy individuals minute volume may be decreased 10–15% and respiratory rate may be unmodified or increased. Oxygen consumption decreases 8–10%. Alveolar carbon dioxide tension increases 2–3 mm. and the blood carbon dioxide capacity remains within 4 vol.% of the control value. The response to carbon dioxide in the inspired air is decreased and the blood remains neutral or shifts 0.05 pH toward the acid side, but experiments are recorded also where respiratory minute volume and oxygen consumption increase and all authors are concordant with respect to a low respiratory quotient after morphine.

While there is no definite evidence of a marked effect of therapeutic doses of morphine on the respiration of a normal man, this does not deny that toxic doses of morphine may cause a fatal interference in the respiration of man or that therapeutic doses of morphine may induce extreme respiratory depression in certain sick individuals. It does mean that the effects of therapeutic doses of morphine on factors concerned in the regulation of respiration in healthy individuals are not the proper source for data to explain such acute effects as may occasionally be observed clinically. Tentatively we would suggest that whenever morphine depresses respiration it does so by decreasing metabolism, by a mechanism involving an increase in hydroxyl ions, or by both (1).

III. Analgesia

Analgesia refers to the blunting of pain. *Narcosis* refers to analgesia accompanied by sleep or stupor. A simple analgesic differs from a narcotic in that it relieves pain without producing stupefaction or unconsciousness. Small doses of narcotic drugs are mainly analgesic; small doses relieve pain without necessarily inducing sleep. *Anesthesia* means the loss of all types of sensations, which in turn means loss of awareness or loss

of consciousness. The action of a narcotic drug differs from that of an anesthetic in that pain is relieved before other sensations are significantly altered or in that by administering a properly selected dose, analgesia may be obtained without stupefaction or sleep. Sleep produced by somnifacient drugs is called *hypnosis*. *Sedation* is a milder degree of hypnosis where the patient is merely calmed or quieted.

Narcosis is also frequently used to designate the general depressant phenomena produced by drugs. The word *ναρκωτικός* was used by Galen for a group of drugs, among which he listed opium. Narcotic properties are frequently thought of as the properties of opium. The Harrison Narcotic Act widened the definition legally to include addicting drugs.

1. Measurement of Analgesia in Man

Since pain is a mental or psychological phenomenon, it is difficult to obtain information concerning pain from animals other than man and studies on man are absolutely essential. In man one can compare pain perception, muscular response to pain (pain reflexes), and pain interpretation (mental responses to pain).

It is easy to establish the truth or falsehood of the qualitative statement that a given drug has pain-relieving properties. It is much more difficult to establish that one analgesic is more valuable than another. Comparison of the clinical value of analgesic drugs requires quantitative data for the evaluation of analgesic properties and of undesired side effects.

A great step forward was taken by the introduction of the quantitative method of Hardy, Wolff, and Goodell (33). The blackened foreheads of subjects were exposed to three seconds' radiation, from a 1000-watt bulb, measured in g.-cal./sec./cm.^{2}. The threshold at which trained subjects just felt pain at the end of the exposure was reported to be constant and independent of the emotional and physical state of the subjects, and the intensity of the stimulus required to produce pain was the same regardless of the size of the skin area stimulated. Hardy, Wolff, and Goodell used themselves as subjects.

The pain threshold was progressively elevated as the dose of morphine was increased from 0.5 to 30 mg. The duration of the decreased sensitivity to a painful stimulus was prolonged as the dose of morphine was increased. Psychologic, hypnotic, and other side effects experienced with morphine were not clearly related to the analgesic action, but began and ended independently. Ischemic pain, obtained by inflating a sphygmomanometer cuff over the upper arm to 200 mm. of Hg pressure, of approximately 40 min. duration immediately before the administration of morphine, reduced the pain threshold raising property to an almost negligible amount. If the ischemic pain was begun at the time of the morphine injection and con-

tinued for 40 min., the duration of the rise in threshold to thermal irradiation pain was reduced. Ischemic and other pains also reduced the intensity and duration of the psychological effects which followed morphine administration (33).

Isbell (5, 6) found the elevations of thermal irradiation pain threshold by morphine in normal subjects and in post-addicts to be comparable, variable, unpredictable, and usually much less than those reported by Hardy, Wolff, and Goodell (33). Frequently no significant rises were produced by morphine and occasionally the pain thresholds were lowered. After a suggestion had been made to non-addicts that they would be given morphine, injection of saline produced rises in pain threshold which were comparable to those produced by morphine. Epinephrine caused a precipitous fall in pain threshold when administered to certain subjects at the time when the threshold-raising effects of morphine were near maximal. Unexpected searches of the persons or belongings of post-addicts by the custodial staff, together with hints that the subjects had engaged in illegal activities, produced intense emotional disturbances. Here morphine failed to elevate the pain threshold of some subjects in whom rises in pain threshold could be demonstrated more or less consistently after injection of morphine under normal conditions. Occasionally morphine actually lowered the pain threshold after such emotional disturbances.

Hardy and Cattell (34) were unable to demonstrate elevations of radiation pain threshold, significantly greater than those affected by placebos, with 300–900 mg. of acetylsalicylic acid (aspirin), 10–45 mg. of codeine, or 20–60 mg. of meperidine. They concluded that untrained subjects, even of high intelligence, cannot be used successfully to measure the threshold-raising effects of aspirin, codeine, and meperidine in the amounts given. Hardy *et al.* (33) had previously found threshold increases in themselves with aspirin and codeine.

In the hands of Denton and Beecher (35), the data on pain thresholds obtained by the Hardy-Wolff-Goodell technique contained gross inconsistencies. Some thresholds were higher after the injection of isotonic sodium chloride solution; some were lower after the administration of morphine; and these discrepancies were common. These inconsistencies were apparent even when a physician with years of experience with the technique tested the subjects who were intelligent, cooperative, college men drilled in the technique before the study started. In the study of Denton and Beecher, the pain threshold was determined before and 90 min. after the injection. There is a possibility that the discrepancies between Hardy, Wolff, and Goodell and Denton and Beecher are due to slight differences in procedure. Hardy *et al.* (33) obtained pain thresholds at 30-min. intervals. It would be very worthwhile to repeat the Hardy-Wolff-Goodell

procedure to see if reasonable *time curves* of threshold alteration might be obtained in different subjects. Denton and Beecher (35) chose 90 min. post-injection because this represented the peak time of analgesia with 10 mg. of morphine from the data of Hardy, Wolff, and Goodell. Average duration of effect has a wide standard deviation as is indicated by differences of 0 to 800 min. in the duration of drowsiness after morphine from the data of Denton and Beecher. It could be that Denton and Beecher chose a post-injection time such that pain depression had subsided in some subjects and had even been replaced by hyperalgesia.

It is not always clear whether the increased pain perceptual threshold under analgesic drugs is a result of changed mental attitude, lack of attention, lack of interest, or lack of careful discrimination, which are themselves factors in the complex act of perception (5). The pain threshold can be elevated as much as 35% by suggestion and hypnosis. There is the possibility that the personalties of the observers, as well as of the subjects, may be involved. The pain threshold in man may be elevated, lowered, or not changed at all by analgesic drugs. This contrasts with the relative uniformity of pain-relieving action of analgesics which is observed clinically. After frontal lobotomy, pain may be relieved and yet wincing or head withdrawal reactions to radiation pain may be intensified. Thus, neither effects on pain threshold nor effects on measurable physiologic responses to painful stimuli have been reliable indicators of analgesia, nor have they measured the analgesic component added by the reduction of anxiety through a reevaluation or failure to evaluate mentally the meaning of pain (5).

Inability to obtain consistent data with the Hardy-Wolff-Goodell technique led Beecher and his coworkers (36) to develop new methods of assay involving clinical analgesia. The methods developed by Beecher and his coworkers constitute another very valuable contribution to the quantitative study of analgesia. There are large variations in the intensity and manifestations of clinical pain, and narcotic agents given intravenously to patients often produce relief of discomfort without significantly altering the perception of pain. Experimentally produced pain can be used to measure the perception of painful stimuli, but not changes in the psychic modification or elaboration of those stimuli. The appraisal of analgesic power must ultimately be based on the capacity of the agent under trial to relieve naturally occurring pain—pain that is a consequence of disease or trauma. Although there is frequent failure of the order of pain to correlate with pathological processes, clinical pain of groups of patients can be measured and expressed quantitatively in terms of its relief by a standard narcotic.

To study clinical pain, groups of 25 to 30 patients were selected during the first 30 hr. following a major surgical procedure in which sufficient