SITES AND MECHANISMS OF ACTION OF MORPHINE AND RELATED DRUGS IN THE CENTRAL NERVOUS SYSTEM[1]

ABRAHAM WIKLER

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[1] From the National Institute of Mental Health of the National Institutes of Health, Public Health Service. (Research Branch, U. S. Public Health Service Hospital, Lexington, Kentucky.)

INTRODUCTION

In the present review, the literature which has appeared during the past decade (up to August, 1950) will be examined with special reference to sites and mechanisms of action of morphine and related drugs in the central nervous system. The literature prior to this period has been reviewed critically in the exhaustive monograph by Krueger, Eddy and Sumwalt (198). Although occasional overlap will be unavoidable for the sake of continuity, no attempt will be made to include references covered by these authors. In the organization of the material it has been deemed advisable for the sake of clarity to separate the data into two groups, one on the acute effects of drugs and the other on the phenomena of tolerance and physical dependence. The literature on acute effects will be considered under separate headings indicative of the presumptive site of action of the drugs under consideration, although it will be apparent that such divisons are rather arbitrary. The general plan will be to present in sequence the data on morphine and other analgesics, the effects of drugs with comparable actions, a consideration of the neurophysiological mechanisms underlying the functions affected by the drugs, and a discussion of the mode of action of the agents under consideration. The literature on tolerance and physical dependence will be considered from the standpoint of sites of origin of these phenomena and the mecha-

nisms involved. This plan of presentation is deemed useful because (a) it provides clues to the nature of the specificity of action of opiate-like analgesics; (b) by analogy, it helps elucidate specific neurophysiological mechanisms underlying some actions of opiate-like drugs; and (c) it helps point up the gaps in our knowledge concerning the mechanisms of action of opiate-like drugs, and suggests new approaches that might be used in research. In this review, the terms "stimulation" and "depression" or their equivalents will be used only in a descriptive sense to refer to augmentation or diminution of any given phenomenon without reference to underlying mechanisms such as depression or excitation of inhibitors or facilitators, except where direct experimental evidence justifies such interpretations.

Section One. Acute Effects

I. CEREBRAL CORTEX

A. Sensory Functions

1. Pain. Introduction

While the pain experience appears to be integrated partly in the diencephalon and midbrain (Walker, 338), certain aspects of it are undoubtedly cortical (Wolff, 372). Goetzl, Burrill and Ivy (135) have recently summarized most of the methods that have been used in the study of analgesic action of drugs. In general, the stimuli employed are: mechanical (sharp point, broad pressure), thermal (heat by conduction or radiation, and cold by conduction), chemical and electrical (faradic and galvanic, condenser discharge, etc.). The receptive fields to which stimuli are delivered include: skin, cornea, tail, conjunctiva, ear, lips, birth canal, scrotum, and tooth. Standard responses which are measured consist of: verbal reports, lid reflex, sharp cry, defensive movements, squeaking, squealing, flight, galvanic skin responses, limb withdrawal, muscle twitch, tail flick, tension of neck muscles, pupillary reflex and movements of the whole body. From the standpoint of localization of action in the nervous system, only the responses offer possibility of analysis. Of these, cortical functions are certainly involved in measurements of "pain threshold" in man which are based on verbal reports of pain perception. As will be shown in other sections of this review, "physiological" reactions to painful stimuli are integrated, in part at least, subcortically and, in some instances, are profoundly affected by drugs in animals with cortex removed, or in spinal animals. For convenience, however, the effects of drugs on both "pain threshold" and "reaction to pain" will be considered.

a. Morphine and morphine-like drugs. The study of analgesia has been given great impetus by the widespread adoption of the method of Hardy, Wolff and Goodell (145) for the measurement of pain threshold in man and this method has also been applied to the study of analgesia in animals (Andrews and Workman, 17; D'Amour and Smith, 73; Ercoli and Lewis, 108). In man, Hardy, Wolff and Goodell (*loc. cit.*) employed radiant heat which could be varied and measured accurately and which was directed at a blackened spot on the forehead for a fixed duration (3 seconds). With increasing intensity of heat, a level was at-

tained at which the sensation evoked changed from heat to prickling. This "pain threshold" was found to be about 0.231 gram cal./sec./cm.^{2} with a standard deviation of plus or minus 2 per cent, and varied only plus or minus 12 per cent within a period of over a year. In contrast, the "alarm" reaction to pain (measured by the electrodermal response threshold to radiant heat stimuli) was variable and affected by emotional states, fatigue, etc. (Hardy, Wolff and Goodell 146). Morphine, codeine and other opiates elevated the pain threshold up to 105 per cent (dilaudid) and also reduced greatly the "alarm" reaction (flight-fight-anxiety) to the stimulus, according to these authors (373). Epinephrine, or pain induced at a time before the threshold-raising action of the opiates was near its peak, reduced greatly the effects of the drugs. These investigators believed that the analgesic action of opiates was due to three factors: elevation of the "pain threshold," reduction of the "reaction to pain," and the promotion of sleep. The reduction of the "reaction to pain" was considered to be the most important factor—the subject still perceived pain but did not care about it.

In post-addicts, however, Andrews (14) obtained variable results with this method. The highest rise in pain threshold, even after administration of as much as 100 mg. of morphine, was less than 15 per cent. In some, the pain threshold was even lowered, contrary to the statement of Hardy, Wolff, and Goodell (146). Yet clinical experience indicates that morphine is just as efficacious in relieving pain in post-addicts as it is in non-addicts. Hence Andrews concluded that elevation of the pain threshold is the least important aspect of morphine analgesia and inferred that post-addicts must have some irreversible changes in the nervous system as a result of previous addiction to opiates. In contrast, Andrews (15) found that morphine reduces changes in skin resistance following exposure to radiant heat to a degree comparable to that in non-addicts. He is therefore in agreement with Hardy, Wolff and Goodell with respect to the importance of the "alarm" reaction in morphine analgesia.

Isbell (179), however, found that the elevations of pain threshold, as measured by the Hardy-Wolff-Goodell technic, which were produced by morphine in both non-addicts and post-addicts were comparable and in both groups of subjects, were variable and unpredictable. When elevations of pain threshold were observed, they were usually much less than those reported by Wolff, Hardy and Goodell (373). Frequently no significant rises were produced by morphine and occasionally the pain threshold was lowered. After the suggestion was 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 this agent was administered to certain subjects at a time when the threshold-raising effects of morphine were maximal or nearly so. Isbell (*loc. cit.*) also investigated the effects of emotional disturbances on the threshold elevating action of morphine. In post-addicts, unexpected searches of their persons or belongings by the custodial staff of the hospital, together with hints that the subjects had engaged in illegal activities, produced intense emotional disturbances which were relieved promptly by reassurance after conclusion of the experiment. Following this

procedure, 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. Similar effects were observed when the emotional disturbance was induced at a time when the threshhold raising action of morphine was at or near its peak. Subcutaneous injection of 5 mg. of methadone under normal conditions elevated the pain threshold only 17 per cent or less.

Other investigators have encountered similar inconsistencies in measurements of pain threshold with the Hardy-Wolff-Goodell technic. Denton and Beecher (85) found that ". . .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." In normal subjects, Chapman and Jones (65) found marked variations in the pain threshold as defined by Hardy, Wolff and Goodell. When motor reactions (muscle contraction at the outer canthus of the eye, or wincing) were used as thresholds, more consistent data were obtained.

Ivy, Goetzl and Burrill (184) adapted the method of Koll and Reffert (193) to man, using an electrical stimulus applied to a tooth filling with a monopolar lead. The voltage at which a verbal report of pain was made by the subject was considered to be the threshold. In 14 subjects, the threshold was lowered in 7, unchanged in 1, and elevated in 6. The rises were up to 0.08 volts (control mean absolute value not given). Using a similar method, Isbell and Frank (179) found that this first sensation was like a tap on a tooth, rather than pain. With higher voltages, definitely painful sensation, described as "aching" or throbbing, were induced but the first tapping sensation merged so gradually with the painful sensation that no consistently reproducible second, or painful threshold, could be determined. At voltages three times the "threshold" voltage, the sensation evoked was definitely painful. After 10 to 20 mg. of morphine in both post-addicts and non-addicts, rises in the first threshold seldom occurred, and the investigators felt that such changes were due to factors which were not under the control of the experimenter. The ability to estimate intensity of pain at voltages three times threshold was not impaired by morphine.

Using a modified Von Frey technic (weighted horse hairs or steel wire bearing 0.0125 to 10 gram weight and attached to a small needle which was applied to spots on the eyelids and lips), Seevers and Pfeiffer (300) were able to obtain reproducible pain perception thresholds which were elevated by opiates. The authors emphasize the distinction between analgesia and narcosis; scopolamine produced narcosis with actual increase in sensitivity to pain as tested by this method. This technic was improved subsequently by Seevers and coworkers (301).

Pfeiffer and coworkers (266) distinguish three kinds of pain: "Supain" is defined as superficial epicritic pain such as that produced by exposure of the skin to radiant heat; "deepain" is such as is evoked by electrical stimulation of a tooth; "sympain" is the painful sensation which is induced by thermal irradia-

tion of a nail bed. Evidence is presented which indicates that the latter is mediated by sympathetic fibers. In man, heroin was found to elevate the "supain" threshold and to have no effect upon the "sympain" threshold. The thresholds for each type of pain were elevated by *l*-methadone.

Denton and Beecher (85) and Beecher, Keats and Mosteller (27) have developed a statistically reliable method of evaluating the analgesic potency of drugs on the basis of their efficacy in relieving post-operative pain in patients. The degree of relief of pain which is effected by various amounts of the drug under investigation is compared with that of a standard dose of morphine. Such a method is of great practical advantage in the empirical evaluation of analgesics since it utilizes "clinical" instead of experimentally induced pain.

Schwartz and Laslo (293) described an analgesimetric method which is based upon digital vascular responses to condensor shocks applied to the foot in man. They found that opiates elevate the threshold of the vasoconstrictor response and reduce the blood flow response.

In animals, opiates and other analgesics produce a rise in threshold of observable reactions to presumably painful stimuli although, as noted, the relation of such reactions to the pain experience is open to question. Definite rises in such reaction thresholds after administration of opiatelike drugs have been reported by investigators using the following technics: (1) Skin twitch (cutaneous maximus muscle response) in dogs on thermal irradiation of the skin of the back (Andrews and Workman, 17). (2) Skin twitch and generalized flight-fight reaction to thermal irradiation of the skin in rat (Ercoli and Lewis, 108). This method was modified by Cahen, Epstein and Krements (60) to facilitate rapid screening. (3) Tail flick in response to local thermal irradiation in the rat (D'Amour and Smith, 73). (4) "Dancing"of mice on a hot plate kept at constant temperature (Wolfe and MacDonald, 371). (5) Vocalization or struggling of cats in response to graded pressures applied to the tail (Eddy, 103). (6) Widening of the palpebral fissures in the dog in response to electrical stimulation of the skin through multiple pinpoints covering a chosen area (Knowlton and Gross, 190). (7) Twitch of the ipsilateral side of the lower lip or head turning in response to stimulation of a canine tooth through bipolar electrodes applied to double amalgam fillings in the dog (Koll and Reffert, 193; Goetzl, Burrill and Ivy, 135; Wikler and Frank, 359).

b. Other Drugs. With the thermal irradiation technic in man, Wolff, Hardy and Goodell (374, 376) observed that acetylsalicylic acid elevated the pain threshold up to 35 per cent. Maximal effect for single doses were achieved by the oral administration of 0.3 gram of the drug. Although acetylsalicylic acid elevated the pain threshold, the heat perception threshold was lowered. Acetanilid, acetophenetidin and aminopyrine had comparable effects on the pain threshold. Trichloroethylene elevated the pain threshold 45 per cent. "Evipal" (0.5 gram) elevated the pain threshold only about 20 per cent although hypnotic and sedative effects were marked. In contrast to morphine, the threshold-raising effects of these agents were reduced only about 25 per cent by induced pain.

That acetylsalicylic acid produces a rise in pain threshold has been questioned

by several investigators. Sonnenshein and Ivy (317) observed no rise in threshold after acetylsalicylic acid with either the thermal irradiation or tooth pulp stimulation technics in man. Similarly, neither Ercoli and Lewis (108) nor Cahen, Epstein and Krementz (60) were able to demonstrate rises in reaction threshold with their respective technics in rats. Using the thermal irradiation technic in untrained subjects, Hardy and Cattell (149) were unable to demonstrate elevations of pain threshold which were significantly greater than those effected by placebos, after administration of 0.3 to 0.9 gram of acetylsalicylic acid, 10 to 45 mg. of codeine or 20 to 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."

Wolff, Hardy and Goodell (375) studied the effects of alcohol on the pain threshold and the "alarm reaction" (measured by the electrodermal response) in man. The pain threshold was elevated about 45 per cent and this was not reduced by pain, in contrast to morphine. The electrodermal response was also reduced and the authors associated this finding with the observed indifference of the subjects to pain.

In addition to drugs which have long been known to possess analgesic properties, other agents have been shown to have such actions by various methods which have already been described. These include observations on the effects of intravenous injections of pentobarbital (Keats and Beecher, 187) and inhalation of nitrous oxide (Chapman, Arrowood and Beecher, 64) in man, mephenesin in patients with causalgia (Stephen and Chandy, 323), and epinephrine in dogs (Leimdorfer and Metzer, 204; Ivy and coworkers, 183). Some investigators have attributed at least part of the analgesic action of morphine to the release of epinephrine through sympathetic stimulation (de Bodo and Brooks, 35) since they found that in rats, elevations of pain reaction thresholds produced by morphine were markedly decreased after adrenalectomy (Friend and Harris, 119); Puharic and Goetzl, 271), Nickerson and Goodman (258) found that in man, amphetamine elevated appreciably the pain thresholds as measured either with the Hardy-Wolff-Goodell technic or the tooth stimulation method, and had a marked effect in elevating the time required for pain (deep pain) to develop on immersion of a hand in ice water. Meperidine had greater threshold raising effects when the radiant heat and tooth stimulation methods were used, but less effect than amphetamine with the ice-water technic. With the last mentioned procedure, synergism between amphetamine and meperidine was demonstrated, but not with the other agents used. Synergism between the effects of amphetamine and morphine in man have been reported by investigators employing the radiant heat technic (Himmelsbach, Ruble and Lloyd, 168) and the tooth stimulation method (Ivy, Goetzl and Burrill, 184); Goetzl, Burrill and Ivy, 136). Slaughter, Parsons and Munal (311) have suggested that the analgesic properties of morphine may be attributed, in part at least, to its cholinergic action (Eadie, 100; Bernheim and Bernheim, 32), since they have observed potentiation of morphine by neostigmine in the relief of pain clinically. Flodmark

and Wramner (115) also reported morphine-neostigmine synergism. Andrews (12) found that in post-addicts and in non-addicts the combination of morphine with neostigmine methylsulfate was not significantly more effective in raising the "pain threshold" to thermal irradiation than morphine alone. However, in cats (Slaughter and Munsell, 310) and in mice (Wramner, 377) potentiation of morphine effects by neostigmine has been demonstrated.

c. Effects of drugs on neurophysiological mechanisms underlying pain. The factors that are involved in the alteration of "pain threshold" in man have not been resolved satisfactorily. Several experienced investigators in the fields of pain and analgesia have commented on the complexity of the problem. Thus Bishop (33) states, "It is not clear in view of the obvious central effects of drugs whether they have any effect on the periphery in ordinary analgesic dosage, nor is it always clear whether the increased perceptual threshold under drugs, etc. is in effect a result of changed mental attitude, lack of attention, interest, or careful discrimination, for instance, which to be sure are themselves factors in the complex act of perception itself." Cattell (62) has commented, ". . . It may well be that the threshold raising effect is secondary to influences on the mental state of the subject, who otherwise is likely to be preoccupied with the painful experience. Just as environmental distractions cause a rise in pain threshold, so do mood changes or the interference with mental processes through drug action. The rise in threshold which may accompany analgesia must then be looked upon as incidental to the changes in mental function, with awareness of pain not necessarily altered. . . ." Objective demonstration of the effects of emotional states on the pain threshold and the action of drugs thereon has already been referred to (Isbell, 178). In addition, Wolff and Goodell have shown that the pain threshold can be elevated as much as 35 per cent by suggestion and hypnosis. Wolf (370) has shown that even the action of peripherally acting drugs can be enhanced, reduced or reversed by suggestion or variations in emotional state. The same problems would appear to apply to estimation by subjects of intensities of pain in terms of "dol" scales (Hardy, Wolff and Goodell, 147).

Another pertinent problem is the relationship of elevation of the pain threshold to the relief of pain which is afforded by analgesic drugs. As noted above, after the administration of analgesic drugs, the pain threshold in man, measured either with the Hardy-Wolff-Goodell apparatus or by tooth stimulation, may be elevated, lowered or not changed at all. This contrasts with the relative uniformity of pain relieving action of analgesics which is observed clinically. Wolff, Hardy and Goodell (373) have emphasized repeatedly that the pain threshold elevating action of these drugs is of less importance in the relief of pain than their action on "reaction to pain". In some experiments (375) these investigators have utilized the electrodermal response as a measure of the "alarm" reaction, which is presumed to be an important component of the reaction to pain. Hardy and Furer (148) have observed that in normal subjects, the electrodermal responses to graded standard pains induced by thermal irradiation were variable, influenced by adaptation and emotional factors and sensitive to extreme changes in the temperature of the environment; the subjects could not predict the degree

of their responsiveness to the pains or correlate it with estimates of their emotional states.

While the electrodermal response to nociceptive stimuli is *a* reaction to pain, it is not at all evident that this response reflects an important or indispensable component of the subjective experience of pain. Isbell (178) has shown that hypnotic doses of pentobarbital elevate the threshold of the electrodermal responses to heat stimuli to a degree comparable with that produced by opiate drugs. Although the intensity of heat stimuli used by this investigator were usually below those necessary to elicit the pain threshold, it may be inferred that pentobarbital would also reduce the electrodermal responses to intensities of heat which are painful. In analgesic states induced by hypnosis in man there are no changes in the cold pressor response (Sullivan, 325) or the blood pressure, pulse rate, respiratory and electrodermal responses to pinprick (Brown and Vogel, 52). Furthermore, Chapman, Rose and Solomon (66) have demonstrated that, after frontal lobotomy, pain may be relieved and yet wincing or head withdrawal reactions to heat pain may be intensified. It appears, therefore, that neither effects on pain threshold, nor effects on measurable physiologic responses to painful stimuli are highly reliable indicators of analgesia. Similar considerations would apply to the use of digital vascular responses to painful stimuli for the measurement of analgesic potency of drugs (Schwartz and Laslo, 293).

The relation of "euphoria" to analgesia has been discussed by Oberst, Reichard, Lee, Clark and Himmelsbach (261). These authors believe that the euphoric and analgesic effects of drugs can be separated since the effects of such drugs on mood vary considerably in different individuals, whereas relief of pain is experienced much more uniformly. The effects of opiate analgesics on mood appear to be in the nature of reduction of ego control over underlying personality traits (Wikler, 351). In post-addicts who volunteer for experimental studies on the effects of morphine and similar drugs, analgesia and euphoria after administration of these agents almost always appear concomitantly, and the degree of euphoria thus produced can be used as a rough measure of the analgesic potency of the drug under investigation (Isbell, 178).

These observations, and the universally recognized fact that opiates alter the attitude toward pain, suggest that an important factor in the analgesic action of these drugs is the reduction of anxiety induced by the anticipation of pain. Hill, Kornetsky, Flanary and Wikler (162) found that, in post-addicts, hand reaction times to visual stimuli were at first shortened and later prolonged greatly by repeated, self-administered penalizations of slow responses by strong electric shocks delivered to the opposite hand. During the first 1½ hours after subcutaneous injection of 15 mg. of morphine, the prolongation of reaction times by electric shock penalties was reduced significantly; indeed, after the administration of morphine in some subjects, reaction times were even faster than the control values in spite of repeated penalization by electric shocks. Evidence was adduced which indicated that such effects of morphine were not related to elevation of the threshold for perception of pain or directly observable immediate reactions to the electric shocks. These investigators concluded that morphine reduces the

disruptive effects on performance which are associated with the intense anxiety which is produced by the anticipation of pain.

These observations suggest a new line of approach to the problem of "psychogenic" pain. When a dog is trained to respond to a bell in anticipation of a painful shock to a limb, it displays evidence of anxiety or suffering in anticipation of shock, but there is no reason to believe that it is experiencing pain itself. Evidently it is not the unconditional stimulus, pain, which becomes conditioned, but the adaptive reaction thereto, namely anxiety or suffering (Wikler, 351). Perhaps "psychogenic" pain is actually conditioned "suffering" and is interpreted as pain by the patient because it was associated with pain at one time. Indeed, psychiatric studies of patients with recurrent causalgia long after the initial trauma indicates that exacerbations of this experience may be produced by conflicts arising from disturbing situations (Kolb, 192). The work of Malmo and Shagass (225) indicates that, after frontal lobotomy, random finger movements during intervals between exposures of the subject to heat pain are reduced, but not head withdrawals and other observable reactions to the painful stimuli. The finger movements can be interpreted as conditioned phenomena associated with anticipation of pain, and their reduction after frontal lobotomy suggests that this operation reduces the strength of conditioning of responses to the suffering associated with pain.

Little is known concerning the neural mechanisms involved in analgesia. The separation of suffering from the pain experience which is effected by opiates and frontal lobotomy suggests that similar mechanisms are operating in both instances. The effects of frontal lobotomy are commonly attributed to interruption of thalamic impulses radiating to the frontal lobe. However, since much evidence points to the diencephalon as the center regulating the state of consciousness and awareness (Penfield, 264), the effects of frontal lobotomy may well be interpreted in terms of interruption of impulses from the frontal lobe to the diencephalon. It may be presumed therefore, that opiates achieve this result by an action on the frontal lobe. That reverberating activity in closed internuncial chains is intimately related to the pain experience, has been suggested on the basis of clinical experience by Livingston (213), and on experimental and theoretical grounds by McCulloch (247). Supportive evidence for this concept is afforded by the observation of Porter and Taylor (270) that the flexor reflex in the spinal cat is facilitated markedly by stimuli which are themselves innocuous (blowing on the fur, etc.). The reported efficacy of electroshock in relieving phantom limb (Pisetsky, 268) and causalgic (Radovici and Wertheim, 272) pains may be explained on the basis that refractoriness in internuncial neurones after synchronous discharge terminates reverberating activity in them. As will be shown below, there is considerable evidence that opiates exert selective depressant actions on after-discharge, which is mediated in part through closed internuncial chains (Lorente de Nó. 222).

Another formulation of the action of analgesics on pain threshold may be made on the basis of an assumed "cortical excitatory state" (CES). It appears reasonable to postulate that the recognition of the pain threshold in man is a

discriminative function for which an optimum cortical excitatory state is required. Emotional disturbances, pain, etc. may raise pain threshold by elevating CES while analgesics may raise threshold by lowering CES, in both cases away from the optimum level required for most precise discrimination. Therefore, the net effects of analgesics or other drugs on pain threshold in any individual under a given set of circumstances (*e.g.*, tranquil, in pain, emotionally disturbed, etc.) may be in the direction of increase or decrease in discriminative ability and hence the pain threshold may be elevated or lowered by the drug or drug combinations used. Such a concept, while only a restatement of the fact that mental factors modify the effects of drugs on "pain threshold", may be useful in planning further investigations.

2. *Sensations other than pain.* Andrews (13) reported that auditory thresholds (audiometer readings) were not altered during repeated administration of morphine to post-addicts. Visual thresholds, however, were elevated to about ten times their original value. This may have been due to reduction of the amount of light falling on the retina consequent to the pupillary constriction produced by morphine. Wikler, Wolff and Goodell (358) found that morphine, codeine, alcohol, a barbiturate and acetylsalicylic acid did not elevate thresholds of perception for touch, vibration, two-point discrimination, smell and hearing in man (large doses of acetylsalicylic acid impaired two-point discrimination in some experiments). Because of these negative results, the authors concluded that the analgesics act specifically on pain thresholds. However, this inference may be open to question because of the variable effects of analgesics on pain threshold which have been reported by different investigators (see above). In their studies on vibratory thresholds, Wikler, Wolff and Goodell measured the duration of perceptible vibration on a tuning fork which was suspended by a crossbar from two fingers (Roth "Neurometer"). Toomey, Kopecny and Mickey (333) employed an extremely sensitive electronic vibrator ("biothesiometer") which was applied to the quadriceps area, forearm or forehead. In previously trained subjects, in whom testing was made on the quadriceps, consistent rises in vibratory thresholds after administration of acetylsalicylic acid 1.0 gram were observed in one series of observations but in others, the threshold was either unchanged or lowered in some subjects. In a group of subjects tested over the forearm, only one exhibited a clear-cut rise in threshold, 3 showed initial lowering by a rise in threshold, in 3 the threshold was lowered and in 5 it was unchanged. When testing was performed on the forehead in the same group, there was no change in threshold in 3, and lowering of vibratory threshold in 2, while in the others, the changes were not clear. In a total of 123 subjects tested (apparently all test areas combined) elevation of threshold was observed in 66 per cent, lowering of threshold in 12 per cent and no change in 21 per cent.

It is apparent that all the factors which have been shown to modify pain thresholds and the action of drugs thereon would be equally operating in the measurement of other thresholds such as those of perception of vibratory sensibility. The divergent observations on the effects of acetylsalicylic acid are therefore not surprising.

B. Threshold of responses of cerebral cortex to stimulation

1. Morphine

Clinicians have long observed that ordinary preoperative doses of morphine do not depress the excitability of the motor cortex to electrical stimulation (Walker, 339). Morphine (15 mg.) or methadone (10 mg.) subcutaneously may be used for sedation prior to electric shock therapy in patients without appreciably elevating the threshold for convulsions (Wikler, 343). In a careful quantitative study on rabbits, Tainter and coworkers (329) found that morphine in doses of 10 and 15 mg./kg. did not alter cortical electrical excitability in spite of marked central depressant effects. Masserman (235) reported that direct injection of 1 to 10 mg. of morphine into the cortex or administration of 30 to 100 mg. (total) of morphine intraperitoneally did not alter the excitability of cerebral cortex of the cat to faradic stimulaton. Using larger but subconvulsant doses of morphine, Bubnoff and Heidenhein (53) noted that the threshold of motor responses to cortical electrical stimulation was elevated by the drug in dogs. Hazelton and Koppanyi (153, 154) reported that large but subconvulsant doses of morphine (100 to 150 mg./kg.) in the rabbit exerted effects which were synergistic with the convulsant activities of strychnine, metrazol and picrotoxin. Smaller doses of morphine did not alter the threshold of convulsions induced by strychnine, metrazol or picrotoxin; neither did they exert synergistic effects. Speransky (319) observed that convulsions appeared about two hours after freezing portions of the dog's cortex if this was done under morphine analgesia (subconvulsant doses) but were delayed for several days if the procedure was carried out under chloral. Nims, Marshall and Nielsen (259) confirmed this finding.

2. Other Drugs

Fulton and Keller (121) reported that pentobarbital, unlike "Dial" and amobarbital, depressed the excitability of the motor cortex in the chimpanzee. Tainter and coworkers (*loc. cit.*) found that in the rabbit sodium pentobarbital, sodium phenobarbital, sodium amobarbital, sodium bromide, chloral hydrate, paraldehyde and alcohol all elevated the convulsive threshold to electrical stimulation of the cortex. Masserman (232) found that intravenous or intraperitoneal administration of 20 to 50 mg./kg. of sodium amobarbital did not alter the threshold of the motor cortex to electrical stimulation. In another study, this investigator observed that the responses of the sigmoid cortex in the cat were not materially changed by direct injections of alcohol into this structure but were occasionally augmented by intraperitoneal injection of 1.0 cc./kg. of alcohol. Such excitatory effects of alcohol on the cerebral cortex were abolished by light ether anesthesia. Mephenesin reduces movements evoked by stimulation of the cortex (Kaada, 186). It is also interesting to note that Tainter and coworkers (*loc. cit.*) found that the "stimulant drugs"—cocaine, amphetamine, other sympathomimetic amines and mescaline—all raised the convulsive threshold of the rabbit's cortex to electrical stimulation even while producing motor excitement. Dandy

and Elman (74) observed that in dogs the presence of cerebral lesions enhanced the convulsant effects of absinthe.

From these observations, it is clear that morphine, even in subconvulsive doses which produce general sedation and changes in the electroencephalogram of animals which are in the direction of depression (see above), can facilitate the production of convulsive activity in the cerebral cortex. Other non-volatile sedatives commonly used in clinical practice tend to inhibit such convulsive activity. Paradoxically, some drugs which produce motor excitation may also inhibit convulsive activity of the cortex.

C. "Release" effects

Richter (276) observed that the grasp reflex, which becomes less active as young monkeys mature, is augmented by morphine. This may be interpreted as evidence of cortical depression with release of lower centers in which the grasp reflex is integrated. Allen, Murphy and Meek (4) have presented evidence that the augmentation of vagal tone after administration of morphine is a "release" effect consequent to cortical depression. These authors found that, in normal dogs trained to lie quietly for two hours, the cardiac rate slows to 48 per minute; no further slowing is then produced by morphine. After decerebration by intercollicular section under cyclopropane without ligation of the carotid arteries, the heart rate remained slow even after recovery from the anesthetic. Morphine then failed to slow the heart rate further, yet responsiveness of the vagal center was demonstrated by further slowing after intravenous injection of 0.1 mg./kg. of "neosynephrine." Furthermore, in cross-circulation experiments, morphine administered to the donor dog failed to slow the heart rate of the recipient decerebrated dog whose head only received its blood supply from the donor dog. Tactile placing and the hopping reaction have been shown to be cortically integrated (Brooks and Peck, 41). Wikler (343) observed that such reactions were not depressed by morphine in cats but were slightly impaired in dogs.

In white mice, Leimdorfer (203) observed that the Straub tail reaction can be induced by pressure over the lumbodorsal spine, and that this response was enhanced by morphine or methadone. However, after transection of the cord, the enhancement of the Straub response by these drugs was abolished. He therefore concluded that in white mice the enhanced Straub reaction, as well as the peculiar rigidity manifested by these animals after morphine, was due to "release" of subcortical centers by a depressant action on the cortex.

D. Learning, discrimination and performance. Introduction

Although crude adaptations can be acquired by long-surviving dogs without neocortex, learning and differentiation are primarily functions of the cerebral cortex (Wikler, 352). The effects of drugs on such cortical functions can be investigated provided that the effects of such agents on the conditional response is definitely greater than that on the unconditional response which is integrated subcortically. The effects of drugs on "motivation" must also be considered. The loci or neural mechanisms in the nervous system which correspond to the psycho-

logical concept of "motivation" are unknown. However, it is known that alteration of "motivation" affects both unconditional and conditional responses, the latter more so than the former. Gantt (125) has shown that conditional salivation is not affected by satiation in experiments in which hunger is the motivating factor. However, Wikler (351) observed a tactile-salivary unconditional response in decorticated dogs which was markedly affected by satiation. Gantt (126) has observed that satiation reduces unconditional acceleration of cardiac rate appreciably, but less than conditional tachycardia in adaptive behavior motivated by hunger. From the standpoint of gross localization of the actions of drugs, the relative effects on conditional and unconditional responses only need be considered. The problem of "motivation" arises in attempts to distinguish between effects on differentiation or discrimination *per se* and altered incentive. In addition, of course, the agents used should not affect appreciably the perception of conditional or unconditional stimuli.

1. Morphine and methadone

Brown (50) investigated the effects of morphine upon the Rorschach patterns in post-addicts. After an average dose of 34 mg. of morphine, total responses, number of details, rare details and human movements were increased. Responses to color were also slightly increased but the "Erlebnistypus" shifted in the direction of more human movement than pure color response. Neurotic signs were reduced. Signs of intellectual control, organizational energy and originality were not affected. The author concluded that, under morphine, the personality of post-addicts changes in the direction of introversion in the sense of increased phantasy living, with the attention being directed to inner rather than outer stimuli. Beck (quoted by Brown, 50) suggested that the results could be interpreted in terms of release of fantasy normally held in control; morphine makes it easier for the individual's fantasy to come to the surface—perhaps to engage in autistic living more easily. Vogel (336) found that adult white males addicted to opium, morphine or heroin were significantly more suggestible than non-addicts, as measured by the postural sway test. Brown (51), in a long-term study of morphine addiction in 2 adult white males, found that efficiency (as measured by steadiness, tapping speed, code learning, continuous subtraction, Scripture's block oscillations, voice, hand and electrodermal responses to word stimuli) was decreased by the drug. However, the most striking finding was the reduction in differences in responses to disturbing (drug, sex and crime) and non-disturbing word-stimuli.

Ivy, Goetzl and Burrill (183) reported that in man "therapeutic" doses of morphine lowered flicker fusion frequency and had biphasic effects on choice reaction time; the latter was reduced initially, but after 45 minutes following injection of the drug it was prolonged.

Simon and Eddy (308, 104) studied the effects of morphine, codeine and their derivatives on maze-trained rats. With hunger as a motivation, morphine increased the delay time most markedly. The number of stops, errors and waste time were slightly increased, as was active time. Feeding non-morphinized rats

increased initial delay slightly and active time markedly. Stops and errors were also increased, but there was no definite effect on active time. The authors concluded that the observed effects of the drugs used could not be explained entirely on the basis of decreasing hunger contractions in the stomach and that effects on the cerebrum and the rest of the nervous system played a major role.

Wikler and Masserman (356) investigated the effects of morphine on learned adaptive responses and experimental neuroses in cats. In untrained cats, intraperitoneal injection of 1 mg./kg. of morphine produced initial sedation and loss of appetite for one-half to two hours, after which motor restlessness and increased appetite appeared. Non-morphinized cats which had not been fed for 24 hours before the experiment were then trained (Masserman, 234) to lift the hinged cover of a box to obtain food pellets. This response was then conditioned successively to light, bell and buzzer stimuli appearing in that order. Some cats were also trained to activate these signals and respond to them by pressing a platform switch in order to obtain food. After a period of training, morphine 1 mg./kg. abolished the conditional responses in order of their complexity during the initial sedative phase. During the early period of this phase the animals would eat food if placed in full view, but did not respond to conditional signals. After the first 10 minutes, however, they did not eat food. During the second phase (increased appetite and motor restlessness), conditional responses reappeared in reverse order of their disappearance. At first the animal ate food in full view only, later it responded to the buzzer, still later, to the bell and light and, finally, some cats also operated the platform switch. After recovery from morphine experimental "neuroses" were induced by a motivational conflict between hunger and fear. In the course of the usual testing of conditional responses, a puff of air was directed against the cat's face and, in some cases, a mild electric shock was also given just when the cat lifted the food box in response to the signals. After a few repetitions, this procedure resulted in complete disruption of the learned behavior. Instead of responding to the signals, the cat displayed great anxiety, exhibited apparently purposeless movements, vocalized, or pressed the platform switch repeatedly without responding to the signals thereby evoked. They also resisted attempts at feeding by thrusting their heads into the box containng food pellets. After intraperitoneal injection of 1 mg./kg. of morphine, the "neurotic" behavior abated. During the initial sedative phase, the cats did not eat or respond to signals but during the second phase the animals ate food placed in full view and later also responded to the buzzer, light or bell. After morphine effects disappeared, neurotic behavior returned. One cat did not respond favorably to morphine. Instead, the evidences of anxiety were greatly intensified and the cat made frantic efforts to escape from the apparatus. Significantly, the neurotic pattern of behavior in this cat had been reinforced repeatedly during the previous two years in the course of other studies on experimental neuroses.

It is difficult to interpret these data in terms of localization of action since it is not known whether animals without cerebral cortex but with intact olfactory tracts will recognize food and eat it when hungry. Decorticated dogs with olfactory tracts sectioned but with visual pathways otherwise intact will not do so.

However, since more complex responses (the "neurotic" pattern appears to be the most complex) were affected more readily than simpler ones, cortical effects may be presumed. Whether differentiating functions of the cortex or those subserving "motivation" were impaired cannot be inferred since the latter was affected concomitantly with changes in conditional response. The significance of the atypical responses of the last cat described with become clearer after a consideration of similar studies on dogs.

Wikler (351) studied the effects of 1 to 5 mg./kg. of morphine on the adaptive responses of intact dogs. The unconditional stimulus was a strong faradic shock to one hindlimb; the unconditional responses, flexion of that extremity, changes in respiration and, in some cases, flight reactions. The conditional signals were pure tones of the same intensity (but of different frequencies) and a light. The conditional responses were similar to the unconditional responses with important modifications of pattern which differed from animal to animal but were fairly constant for each dog. Both "positive" and "negative" conditional responses were developed by associating some signals with shock and others not. Differentiation of positive and negative signals was established by training. The ability of dogs to differentiate varied markedly. One stable animal differentiated six different tones between 300 and 500 cycles per second even when some of these were so close together that the experimenter could not recognize them without comparison. Two other animals learned to differentiate even widely differing tones with difficulty. In these animals, "neurotic" behavior was the rule and was easily induced by requiring them to differentiate beyond their capacity. The "neurotic" behavior of one dog was of hyperactive variety with struggling, vocalization defecation and urination, and "panic-inhibition"—immobility during the exhibition of the conditional signal followed by frenzied excitement. In the other dog, the "neurotic" pattern was the reverse—complete unresponsiveness, sagging posture and, at times, cataleptic phenomena. The stable dog could not be made neurotic by pushing differentiation, but did develop excitement and loss of differentiation (responding positively to all tones) when attempts were made to extinguish a strong positive conditional response by non-reinforcement.

The effects of morphine in the doses mentioned or of methadone (2 mg./kg) given at intervals during the course of these studies can be summarized as follows. The effects of the drugs depended on the stability of the conditional response, the effects on the unconditional response and the personality of the dog as manifested by its adaptive pattern under the conditions of the experiment over a long period of time (2 years). In general, the drugs impaired least the stable adaptive patterns, irrespective of whether these were correct responses to "positive" or "negative" stimuli, or "neurotic" responses. Conversely, the drug impaired most the least stable types of adaptive response, again regardless of category. Thus, in the basically "neurotic" animals, morphine or methadone abolished whichever conditional responses they had learned, and "released" the "neurotic" response, the latter being typical and reproducible for each animal. In the stable dog, morphine or methadone impaired differentiation only in the early part of the training period. The motor response was affected

more consistently than the respiratory response. When "neurosis" was produced by attempts at extinction, the drugs ameliorated the neurotic pattern and restored the differentiation. Such differences between the dogs was manifested only in the experimental chamber on presentation of stimuli. In their cages, and in the harness between stimuli, all dogs appeared to be sedated and dozed frequently.

In these experiments the changes produced can be reasonably attributed to cortical effects since the unconditional response was kept constant by adjustment of the strength of the unconditional stimulus (faradic shock). The relation of "personality" to the effects of morphine or methadone offers an explanation of the effects of morphine on the highly "neurotic" cat described by Wikler and Masserman, and also of the wide variation in the effects of morphine on the subjective state and total behavior seen clinically in man (Salter and White, 284; Brown, 49).

2. Other agents

Utilizing a motor response to electric shock in man, Finkelstein, Alpern and Gantt (113) found that differentiation between "positive" and "negative" conditional signals was improved by oral administration of 10 to 30 mg. of amphetamine. The positive responses were not augmented, but there were fewer incorrect positive responses to negative stimuli. Alcohol (1.5 cc./kg. orally) impaired differentiation with an increase in the number of incorrect positive responses to negative stimuli. Respiratory conditional responses were augmented.

Himmelsbach, Ruble and Lloyd (168) studied the effects of amphetamine on post-addicts under conditions which simulated those under which such personalities would take the drug if it were freely available. These subjects asked for and were given subcutaneously doses of amphetamine varying from approximately 50 to 1000 mg. over periods varying from 4 to 30 days. Mood changes were marked. With smaller amounts of amphetamine, euphoria and increased psychomotor activity were observed. With larger doses, irritability, insomnia and listlessness occurred. In 3 subjects, extreme anxiety, panic-states, confusion or paranoid delusions occurred. Psychological testing could not be performed on these subjects. However, in a group taking morphine and amphetamine in combination, such studies indicated an improvement in those tests in which speed was a factor, as compared to a control group receiving only morphine, and this was attributed to the amphetamine.

On the basis of clinical observations, Curran (71, 72) believes that the psychologic changes that occur in barbiturate and in bromide intoxication are different and specific for each drug. In chronic barbiturate intoxication, euphoria and hypomania occur, and are associated with cerebellar neurological signs. In chronic bromide intoxication the mental changes are those of delirium, paraphasic speech disturbances, visual hallucinations "at a distance," confabulatory memory defects, and micro- or macropsia. These are associated with absence of corneal and gag reflexes, tremors and vestibular disturbances (ideas referring to motion of boats or nets).

Kornetsky (194) studied the effects of chronic barbiturate intoxication on 5 former morphine addicts during daily administration of varying doses of secobarbital, pentobarbital or amobarbital which were sufficient to produce signs of mild to severe intoxication over a period of 92 to 144 days. Included in the studies were scores on digit-symbol, "draw-a-man", Bender-Gestalt, Rorschach, Stanford-Binet, and Koh's blocks tests. In general, scores on tests involving speed in performance were more markedly impaired than those involving chiefly ability to copy or utilize well fixed material in the subjects' past experience. The effects of chronic barbiturate intoxication on responses to the Rorschach cards were in the direction of reduction of ego control, "release" of repressed dynamic processes and general regression to earlier stages of psychodynamic development. Significantly, it was observed that in the 3 subjects who developed psychotic reactions after abrupt withdrawal of barbiturates, the pre-addiction Rorschach patterns were characterized by the fact that constriction was marked and appeared to be the only defense against relatively undifferentiated and primitive drives. During chronic barbiturate intoxication evidences of such poorly handled instinctual material became more prominent in the Rorschach cards and this may have been related to the marked psychic disturbances which occurred in these individuals during abstinence from barbiturates.

In a dog with an excitatory type of experimental "neurosis", Pavlov (263) found that daily administration of 100 cc. of 2 per cent sodium bromide in water per rectum strengthened "inhibitory" responses without diminishing the strength of positive responses. In a "phlegmatic" dog, bromides had no such ameliorating effect *i.e.*, the drug did not improve positive responses. The responses studied were salivary secretion to auditory stimuli with hunger as the motivation. The inference drawn from these observations was that bromide strengthened cortical inhibition. Caution must be exercised in identifying such "inhibition" with the term as used in electrophysiology.

Gantt and Wolff (127) studied the effects of caffeine, amobarbital bromides and chloral on conditional salivary responses in the dog, with hunger as a motivation. To avoid the use of words which imply knowledge of underlying neurophysiological mechanisms, they applied the term "threshold-lowering" to such stimuli which, after training, evoked increased salivary secretion and "threshold-raising" to those that reduced it. Caffeine decreased latency, increased threshold-lowering and reduced threshold-raising effects without impairing differentiation. After the barbiturate, the effects of threshold-raising stimuli were always augmented, but triphasic changes were noted on the effects of threshold-lowering stimuli. Initially, the effects of threshold-lowering stimuli were augmented, then a long-lasting diminution of such effects occurred and during recovery from the drug augmentation reappeared. Differentiation was not impaired. Bromides augmented the effects of threshold-raising stimuli while chloral exerted effects similar to amobarbital.

The effects of various doses of alcohol on conditional and unconditional salivary and motor responses of dogs were investigated by Gantt (123). Oral administration of 0.5 cc./kg. of alcohol in the form of a 20 per cent solution in-

creased the latency of both motor and secretory responses but did not impair differentiation and produced no gross change in behavior. Quantatitive reduction in conditional responses (positive) was observed in two dogs in which these were weak, but no change in a dog with stable conditional responses. Doses of 1.5 cc./kg. did not affect differentiation but produced evidences of slight intoxication. Positive conditional responses were reduced. Doses of 4.0 cc./kg. reduced latency, impaired differentiation and produced gross signs of intoxication. In one dog in which a negative as well as positive conditional responses had been developed prior to administration of alcohol, this drug resulted in the appearance of positive responses to the negative stimuli. With all doses, the unconditional response (salivary and motor reactions after food was taken into the mouth) was relatively unimpaired. The author concluded that alcohol depresses cortical function without impairing subcortical activity.

The same author investigated the effect of alcohol on sexual reflexes (124). In "normal" dogs alcohol (0.5 to 2 cc./kg. orally) increased the latency and reduced the duration of erection evoked by local stimulation (unconditional response). In a "neurotic" dog, the same effects were observed, but on alternate days between administration of alcohol latency was reduced and duration of erection prolonged. Also, the inhibiting effect of the experimental chamber on sexual reflexes was abolished at these times. These observations may be interpreted either as a residual depressant effect of alcohol on cortical inhibition or a secondary augmentation of subcortically integrated sexual reflexes.

Masserman and Yum (241) studied the effects of alcohol on learned adaptive behavior and experimental neuroses in cats, employing the method described above which was used for studies on morphine (Masserman, 221). Various doses of alcohol, given orally with milk in a cocktail glass, reduced or abolished conditional responses in order of their complexity and alleviated the signs of experimental "neuroses". While "neurotic", cats preferred the milk and alcohol mixture, but after "cure" by various methods (Masserman, 238) they preferred straight milk. The effects described may be presumed to be cortical in origin since Gantt (*loc. cit.*) has shown that even relatively large doses of alcohol have little effect on the unconditional response.

In a long-term study of experimental "neuroses" in sheep and dogs, Anderson and Parmenter (9) investigated the effects of various agents on positive motor conditional responses. In general, when the conditional motor response was increased in vigor, spontaneous restlessness between conditional responses was decreased, and conversely, diminution in vigor of the conditional response was associated with increased interval restlessness. Cortin, 0.4 to 0.8 gram, 0.384 to 0.768 gram of phenobarbital daily for nine days and 2.5 gram of sodium bromide per rectum (single dose) augmented the positive conditional responses and diminished restlessness. Epinephrine, sodium amobarbital (0.32 gram intraperitoneally) and alcohol (160 cc. of 40 per cent solution) orally diminished the vigor of conditional responses and increased interval restlessness.

Gantt, Thorn and Dorrance (128) found that in dogs, low oxygen tension equivalent to an elevation of 25,000 feet disturbed differentiation so that positive

responses were made to negative stimuli in experiments utilizing either the salivary or motor reactions.

In a study of motor, salivary and sexual responses of dogs, Alpern, Finkelstein and Gantt (5) found that oral doses of 10 to 30 mg. amphetamine (total) caused increase in latency and diminution in the unconditional salivary and sexual responses and variable effects on the unconditional motor response. Conditional salivary secretion was increased but differentiation was impaired so that the animal responded with increased salivation to negative and weekly positive stimuli. These effects indicate that amphetamne has opposite effects on cerebral cortex and subcortical structures with respect to the functions investigated.

The effects of repeated metrazol convulsions on differential condition salivary and motor responses of dogs were observed by Rosen and Gantt (279). Immediately after regaining consciousness following each convulsion, all conditional responses were abolished. On alternate days between convulsions, different effects were observed on the salivary and motor responses. After the first few seizures, both positive and negative stimuli evoked increased salivary secretion. Later, both types of stimuli evoked very little secretion and the orienting reflex, which is subcortically integrated (Wikler, 352) and is usually inhibited in trained animals, reppeared. The effects on motor conditional responses varied with the personality of the animal. In a previously stable dog, differentiation was markedly impaired so that both positive and negative stimuli evoked positive responses. In a previously excitable, unstable animal, in which no differentiation was developed previously, positive stimuli evoked fewer positive responses but negative stimuli evoked no responses, thus representing an improvement in differentiation as a whole. In all cases, metrazol had little effect on unconditional responses. The authors conclude that repeated metrazol convulsions produce a depression of cortical function, resulting in a combination of reduced responses to positive stimuli and disinhibition of the responses to negative stimuli.

Masserman (239) studied the effects of repeated convulsions induced by cerebral electroshocks on learned adaptive responses and "experimental neuroses" in cats. The effects were quite similar to those of single doses of morphine (Wikler and Masserman, 356) except that after electroshock convulsions there was residual impairment of the capacity for complex adaptations.

Gellhorn, Kessler and Minatoya (132) observed that insulin hypoglycemia and convulsions induced by metrazol or electroshock restored conditional responses which were previously inhibited by extinction in rats. This effect is specific for "internal inhibition" since inhibition induced by other means is not afforded by these agents (Gellhorn, 130). These authors believe that the cortical disinhibition produced by insulin hypoglycemia, metrazol and electroshock convulsions is secondary to autonomic discharges consequent to stimulation of the hypothalamus, since these procedures have different effects on the electroencephalogram. This conclusion does not appear to be justified since in the post-seizure period the electroencephalogram shows evidence of profound cortical depression comparable to that produced by insulin coma.

Funderburk and Case (122) reported that conditioned motor avoidance re-

sponses in cats were abolished by intravenous injection of physostigmine (0.06 to 0.25 mg./kg.), but they were not affected by intraperitoneal injection of neostigmine (0.12 to 0.25 mg./kg.) except indirectly when severe gastrointestinal disturbances were induced. The differences between the observed actions of these drugs was attributed to the fact that physostigmine is a fat-soluble tertiary ammonium base and can therefore penetrate nerve cells, while neostigmine is water-soluble only and hence cannot. Physostigmine depresses chloinesterase activity and therefore produces an increase in cortical acetylcholine content. The authors state that their findings are opposed to those of Gantt and Freile (quoted by Funderburk and Case, 122) who found that acetylcholine caused marked augmentation of conditioned responses.

3. Comparison of the effects of morphine and methadone with those of other agents on learning, discrimination and performance

Direct comparison of the effects of morphine and methadone on learning, discrimination and performance with those of other drugs is difficult because the subjects or animals used cannot be matched for personality, stability of the adaptive responses, duration of training periods and responses investigated. The effects of morphine and methadone appear to depend a great deal on the underlying personality of both man and animals, whereas the effects of other drugs, although frequently differing widely from each other, appear to be less dependent on personality. However, clinical experience with barbiturates, alcohol and amphetamine suggests that personality factors are of great importance in determining the ultimate effects of these agents on adaptive behavior. Possibly in experimental studies, subjects or animals are usually selected on the basis of uniformity in their responses prior to studying drug effects. The need for long-term studies of drug effects on individual subjects or animals, rather than the accumulation of "statistically significant" data from short experiments on large groups, is apparent.

4. Effects of drugs on neurophysiologic mechanisms underlying learning, discrimination and performance

Aside from evidence which has already been pointed out that the agents considered do have cortical actions, the neurophysiological mechanisms by which such effects are exerted are unknown. The use of terminology borrowed from pharmacology or neurophysiology such as "stimulation", "depression", "facilitation" and "inhibition" to describe phenomena concerned with total adaptive behavior is not only unjustified, but actually misleading (Wikler, 353). In all studies on behavior, the problem of motivation is of paramount importance. Practically nothing is known concerning its neuro-humoral basis, although the pioneer work of Richter (277) should stimulate more investigation of this very important problem.

Another field which merits further investigation is that of conditioning of drug effects. Some of the literature has been reviewed by Wikler (351). Attempts to condition the direct effects of peripherally acting drugs such as epinephrine,

pilocarpine and histamine have been uniformly unsuccessful. This is not surprising, since such direct effects constitute the unconditioned *stimulus* and it is the unconditioned *response* only which can become conditioned. One would therefore expect that if the effects of peripherally acting drugs could be conditioned at all, it would be those effects which are in the nature of compensatory or adaptive responses to the direct peripheral actions of such agents. To test this hypothesis, Wikler (*loc. cit.*) gave daily subcutaneous injections of 5 mg./kg. of atropine to dogs and cats. Within a priod of two weeks, conditioned salivation was observed in some of the animals, more uniformly in the cats. These findings were interpreted as evidence of conditioning of a compensatory response (salivation) to the drying of the mouth which was produced by the direct peripheral action of atropine. Mulinos and Lieb (quoted by Wikler, *loc. cit.*), however, had observed this reaction before, and ascribed it to conditioning of a stimulating action of atropine on the medullary salivatory centers.

It is generally believed that the direct effects of drugs which act centrally can be conditioned, *e. g.*, conditioning of the emetic action of morphine in dogs (Pavlov, 263). However, the supposed direct action of morphine on the vomiting center may now be open to question, since Wang and Borison (340) have demonstrated that the emetic action of apomorphine in the dog is a reflex response to stimulation by the drug of chemoreceptors in the dorsal sensory nucleus of the vagus.

E. The Electroencephalogram

While spontaneous rhythmic activity is a property of the cerebral cortex, it should be recognized that many cortical functions are not reflected in the electroencephalogram. Attempts to correlate changes in the electroencephalogrm of man with certain mental disorders, various subjective experiences and finer alterations of consciousness have not been successful. It is quite possible that spontaneous cortical electrical activity is related to functions of specific neuronal systems which are, at least in part, independent of those which subserve ideation, affect, consciousness and perhaps even sensation and motility (Wikler, 355). This inference is supported by an analysis of the action of drugs on the electroencephalogram.

1. Morphine, meperidine, keto-bemidone and methadone

In post-addicts and in most normal men, Andrews (10) found that subcutaneous or intramuscular injection of morphine 20 mg. produced no significant changes in the electroencephalogram. In one non-addict, this dose of morphine produced slow activity characteristic of certain stages of sleep although the subject was definitely not asleep. After repeated doses of morphine in post-addicts, changes appeared in the electroencephalogram. These changes consisted of a lowering of alpha frequency, an increase or decrease in alpha index and the appearance of delta waves (Andrews, 13). The changes in alpha index appeared to be related to that present in the control record. When such activity was low initially, it was increased by repeated doses of morphine; when high initially,

it was lowered by repeated doses of the drug. Delta activity appeared only in the most severely addicted patients. There was no quantitative correlation between changes in the electroencephalogram and state of consciousness. When alpha activity was reduced by morphine, visual stimuli caused the reappearance of alpha rhythms and these were abolished by another light stimulus.

Gibbs and Maltby (133) employed the Grass frequency analyzer in their studies on the effects of single and repeated injections of morphine (16 mg. per dose) on the electroencephalograms of human subjects. At first, morphine caused an increase in voltage of 20 cycles per second activity and later, a shift to the slow side of the 10 cycles per second range with lowering of "total voltage level". It should be noted, however, that the Grass analyzer cannot distinguish between fundamental and harmonic frequencies, or between changes in voltage due to change in number of waves at any frequency and changes in voltage of waves of any given frequency. Also the voltage analysis becomes very complex when the wave form deviates significantly from that of a sine wave.

Wikler (354) found in post-addicts, that morphine 20 mg. intravenously caused no gross change in the electroencephalogram which was apparent by inspection. Scheider and Remond (287) reported that intravenous injection of morphine accentuated previously existing abnormalities. Sleep was not produced.

Andrews (11) studied the electroencephalographic changes during repeated administration of meperidine (up to 2.98 grams over a 70-day period) in 2 post-addicts with normal control electroencephalograms. Early during this period high amplitude delta activity and reduction of alpha activity appeared in the record. The delta activity tended to appear in bursts. These changes became more prominent as the administration of meperidine continued. Concomitantly, both subjects exhibited tremors and gross finger twitches; the latter had no cortical representation as judged by the electroencephalogram. The subjects also exhibited epileptiform and psychotic episodes.

The effects of methadone on the electroencephalogram were studied by Isbell and coworkers (180, 181). Single doses up to 30 mg. had no effect on the electroencephalograms of most post-addicts. In one subject, slow activity appeared. During repeated administration of methadone, progressive slowing of the records occurred, until continuous delta activity dominated the electroencephalogram. The subjects showed a tendency to somnolence but there was no quantitative correlation of the electroencephalographic changes and the state of consciousness. The changes in the electroencephalogram apeared to be similar to, but much more marked than, those reported by Andrews (12) during repeated administration of morphine.

Altschul and Wikler (6) investigated the changes in the electroencephalogram during repeated administration of keto-bemidone. A progressive slowing of the record occurred concomitantly with some increase in the number of low amplitude fast waves. In 2 subjects with previously abnormal electroencephalograms, paroxysmal high voltage delta and also spike and dome activity appeared in the records on a few occasions, without clinical evidences of overt seizures.

In unanesthetized rats, Cahen and Wikler (59) found that morphine up to 20

mg./kg. produced sedation but no changes in the electroencephalogram. After morphine 20 to 50 mg./kg. an increase in voltage and decrease in frequency were noted; later, bursts of 10 to 12 cycles per second spike-like waves continued to appear in the record for several hours. Morphine in doses of 200 mg./kg. or in doses of 40 to 100 mg./kg. combined with pentobarbital 9 to 30 mg./kg. abolished cortical activity but this was restored by oxygenation.

Wikler and Altschul (362) studied the effects of small doses of methadone and morphine in normal dogs and of larger doses in curarized dogs. Methadone 2 mg./kg. or morphine 5 to 10 mg./kg. caused the appearance of irregular high voltage random slow waves in tracings recorded from dural leads. Fast activity present in the control records persisted. Initially after methadone, 75 mg./kg. or morphine 200 mg./kg., high voltage fast activity, tending to appear in bursts, occurred in cortical tracings, without significant changes in tracings from a sphenoid lead. Later, high voltage slow activity appeared also, and this was noted in both cortical and sphenoid tracings. In several experiments, in addition to the changes already noted, paroxysmal seizure discharges occurred. These occurred usually in the cortical tracings without significant changes in tracings from the sphenoid lead. In one record after methadone, a sustained high voltage spike seizure discharge appeared simultaneously in both cortical and sphenoid records. The cortical seizure discharges were either of the spike and dome or the sustained spike variety, the former especally prominent in the morphinized dogs. The spike and dome discharges often appeared first or only in one hemisphere. Bilaterally synchronous spike and dome discharges could be induced by sudden loud noise such as that produced by clapping the hands. After subsidence of a sustained high voltage spike seizure discharge in the sphenoid tracings after methadone, a steady 25 cycles per second moderate voltage rhythm appeared in the same tracings while the cortical records were isoelectric or showed only slow activity. It is noteworthy that the propensity of large doses of morphine to produce "petit mal" seizure discharges was also noted by Wikler and Frank (359) in the electrical patterns of seizure discharges produced by electroshock in decorticated cats.

In the course of investigations on the effects of local freezing on the electrical activity of the cerebral cortex, Nims, Marshall and Nielsen (259) noted that in dogs and monkeys this procedure rarely produced immediate electrical seizure discharges if the procedure was carried out under pentobarbital anesthesia. However, if the procedure was carried out under morphine analgesia (20 mg./kg. in dogs), generalized high voltage spike seizures (dogs) or generalized spike and slow waves (monkeys) always appeared within two and one-half hours after freezing a portion of the cerebral cortex.

It appears probable that these effects were due to the convulsant action of morphine since the time interval (2½ hours) for the appearance of the seizure discharges is about the same as that observed by Wikler and Altschul (362) in dogs without freezing of the cortex. Freezing of the cortex appeared to lower the convulsive threshold since no seizure discharges were noted by Wikler and Altschul with such moderate doses of morphine.

Leimdorfer (203) compared the actions of morphine and methadone on the

electroencephalograms of cats which were either "curarized" with beta-erythroidine or lightly anesthetized with ether. With intravenous injection of increasing doses of methadone, the successive changes in the electroencephalogram in order of their appearance were slowing and single diphasic spikes, bursts of diphasic spikes and finally abolition of cortical electrical activity while the electrocardiogram showed only slight bradycardia. A single intravenous injection of a large dose of methadone produced a high voltage spike seizure discharge. With intravenous injection of increasing doses of morphine, the successive changes were a slight increase in frequency, increase in both voltage and frequency, the appearance of low voltage slow waves, and finally abolition of cortical electrical activity while the electrocardiogram showed only bradycardia. In these experiments, the abolition of cortical electrical activity could not have been due to asphyxia secondary to respiratory depression since the animals were maintained on artificial respiration. However, these changes could have been due to cerebral anemia since it is well known that after intravenous injection of morphine (Schmidt and Livingston, 291) or methadone (Shideman and Johnson, 307) a marked drop in blood pressure occurs.

2. Other drugs

The effects of a great number of agents on the electroencephalogram have been reviewed by Toman and Davis (332). In this section only those effects of drugs not regarded as analgesics will be considered which may help elucidate the mechanisms underlying the effects of the analgesic drugs on the electroencephalogram.

The effects of barbiturates on the human electroencephalogram have been studied by numerous investigators (Gibbs and Maltby, 133; Brazier and Finesinger, 38; Lennox, 205; Brazier, 37). Although detailed effects vary from one individual to another and the dose and mode of administration of the drug influence the changes seen in the electroencephalogram, a fairly uniform pattern of change can be described. Initially, there is an increase in voltage and perhaps amount of fast activity, which may be fairly continuous. During this period the subject is not asleep but he may be euphoric and awareness is impaired. Later, "spindles" of relatively high voltage fast activity appear, chiefly in the frontal leads, and other activity may be slowed. During this period the patient is apt to be asleep or in light surgical anesthesia. With larger doses, the electroencephalogram may show general slowing corresponding to deep surgical anesthesia. Between the initial stage of generalized fast activity and the stage of general slowing, the cortical electrical patterns in general resemble certain stages of normal sleep (Davis and coworkers, 76). During the process of recovery from the anesthetic, the electroencephalographic changes reappear in reverse order. When barbiturates are taken orally in repeated doses over long periods of time the electroencephalogram shows a predominance of relatively high voltage fast activity of a more or less continuous nature with admixture of slow waves. Although such subjects are generally somnolescent, there is no quantitative correlation between the degree of change in the electroencephalogram and that of consciousness (Isbell and coworkers, 182).

In the unanesthetized rat, Cahen and Wikler (59) noted a sequence of changes

in the electroencephalogram following intraperitoneal injection of sodium pentobarbital (total of 48 mg./kg.) which was similar to that noted in man. Initially, there was an increase in fast activity with admixture of slow waves, later the voltage of both types of activity became higher and the fast activity tended to appear in bursts. Later still, slow activity predominated and finally only irregular low voltage activity with random spike-like discharges dominated the records.

The effects of increasing doses of sodium amobarbital and of ether on the cortical electrical activity of the dog has been studied carefully by Swank and Watson (326) and Swank and Foley (325). In the unanesthetized dog at a low level of excitation, the dominant frequencies in the electroencephalogram were about 25 cycles per second. A variable amount of 12 cycles per second activity posteriorly and of 50 cycles per second anteriorly was also present. During ether anesthesia the electroencephalogram was dominated by 50 cycles per second activity. Slow waves appeared only during deep anesthesia. During induction of sodium amobarbital anesthesia 50 cycles per second activity disappeared first, then 25 cycles per second and finally, 12 cycles per second activity also disappeared. Amplitude and frequency were altered least in the motor area. During the lighter stages of anesthesia, "burst" activity similar to that noted by other workers was observed. In deep anesthesia, "suppression-bursts" appeared. These consisted of periods of no cortical activity ("blackouts") alternating with bursts of slow activity. Such "blackouts" could be abolished and cortical electrical activity restored by breathing 100 per cent oxygen.

Beecher and McDonough (26) made a comprehensive investigation on the action of anesthetics on the electroencephalogram of the cat. From their effects on the electroencephalogram these agents could be divided into two groups: (1) relatively volatile substances including nitrous oxide, cyclopropane, ether divinyl ether, ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, chloroform and amylene hydrate; (2) relatively non-volatile substances including tribromoethanol, "evipal", paraldehyde, sodium barbital, chloralosane and pentobarbital. In general, the substances included in group (1) produced low voltage fast activity, while those in group (2) produced higher voltages and slower activity with a tendency to bursts of 1 to 10 cycles per second waves in the electroencephalogram.

Greenblatt, Levin and Schegloff (138) studied the electroencephalogram in man in relation to blood bromide level. High blood levels were associated with slow activity, moderate with mixed fast and slow activity, and low with fast activity.

Williams and coworkers (368, 357) have described the changes in the electroencephalogram of man resulting from smoking marihuana cigarettes and also during chronic intoxication with "pyrahexyl" compound, which exerts clinical effects similar to those produced by cannabis. Smoking marihuana cigarettes produced a marked increase in muscle artifacts in the electroencephalogram. Alpha percentage appeared to be reduced without significant change in alpha frequency. These changes were associated with euphoria, and increased psychomotor activity. Single doses of pyrahexyl compound had little effect on the

electroencephalogram. During repeated oral administration of increasing doses of "pyrahexyl" compound the electroencephalogram became slowed progressively. Early in the study, the subjects were euphoric and exhibited increased psychomotor activity, but later they became listless and somnolescent.

Engel and Rosenbaum (107) reported an increase in slow activity during acute alcoholic intoxication. In cats, Beecher (24) found similar effects, the degree of slowing being directly related to molecular weight (number of carbon atoms in the chain) of various alcohols, and also to anesthetic potency for any compound of given molecular weight.

The effects of the "stimulant" drugs, caffeine, amphetamine and epinephrine, on the human electroencephalogram were studied by Gibbs and Maltby (133). Expressed in terms of the voltage-frequency curve obtained with the aid of the Grass frequency analyzer, caffeine caused a shift to the fast side with reduction of total voltage level, while amphetamine and epinephrine produced a shift to the fast side with increase in total voltage level. The changes were more marked after epinephrine.

The progressive changes occurring in the human electroencephalogram under low oxygen tension were studied by Davis, Davis and Thompson (80). Initially, the per cent time occupied by alpha activity increased in some subjects, but later it decreased and the voltage of alpha waves was also reduced, without change in alpha frequency. With the onset of unconsciousness, delta activity appeared in the record. On recovery of consciousness after rebreathing air, delta activity disappeared and alpha rhythms returned. Brazier (37) reported similar findings but noted that during hypoxia, the alpha frequencies were slowed progressively.

Quite different results were obtained in the cat by Sugar and Gerard (234) after periods of cerebral anemia produced by vascular occlusion. The initial changes in the electrocorticogram following vascular occlusion consisted of increase in frequency and voltage; later, periods of no activity alternating with "spindles" of waves varying in frequency from 6 to 12 cycles per second appeared. The changes were ascribed to anoxia.

In "therapeutic" doses sufficient to reduce extrapyramidal rigidity and relieve "central" pain, mephenesin produces no significant effects on the electroencephalogram of man (Stephen and Chandy, 323). In doses large enough to produce paralysis and marked changes in other functions of the nervous system, mephenesin was found to have no significant effect on the spontaneous cortical electrical activity of the cat (Kaada, 186).

The effects of hypoglycemia on the electroencephalogram of man were described by Brazier (37) In general, the effects were similar to those of hypoxia, namely, a progressive slowing of the frequencies of the alpha activity with no sudden changes until consciousness was lost, when delta activity appeared. However, beta activity, when present, was not slowed. Similar effects of hypoglycemia on the electroencephalogram were observed by Hoagland and coworkers in dogs (170). Marke hdypoglycemia finally abolished cortical electrical activity. This change was reversed by intravenous injection of glucose.

3. Comparison of effects on the electroencephalogram of analgesic drugs with those of other agents

In general, the effects of the analgesic drugs morphine, methadone, meperidine and keto-bemidone on the electroencephalogram are similar, although there are quantitative differences. In man, ordinary analgesic doses usually have no significant effect on the resting electroencephalogram. This indicates that the cortical neural mechanisms concerned with the pain experience are at least in part independent of those which subserve spontaneous electrical activity. The initial increase in frequency with or without increase in voltage which is produced by the anesthetics or stimulant agents (caffeine, amphetamine and epinephrine) is not prominent after administration of the analgesics. Sleep patterns in the electroencephalogram are produced occasionally in man and regularly in animals by the analgesic drugs and also by barbiturates and other non-volatile anesthetics. Generalized gradual slowing of the alpha rhythm occurs during repeated administration of the analgesics, during chronic pyrahexyl intoxication, in hypoxia or hypoglycemia, and less markedly after barbiturates and other non-volatile anesthetics. Diffuse continuous delta activity without marked impairment of consciousness occurs during repeated administration of the analgesics or pyrahexyl compound, alcohols and bromides. Sudden appearance of high voltage delta activity associated with loss of consciousness is not commonly produced by the analgesics but does occur during hypoxia or hypoglycemia. Such changes can be produced by morphine in man by tilting the patient suddenly from a horizontal to a vertical position but this is due to syncope consequent to peripheral vasodilatation (Drew, Dripps and Comroe, 92; Engel, 106). Convulsive activity in the electroencephalogram is produced regularly in animals by large doses of the analgesics and occasionally in man (meperidine; keto-bemidone). Seizure discharges have not been observed in man or animals after the other agents under consideration.

4. Neurophysiological mechanisms underlying the action of drugs on the electroencephalogram

For general orientation, a tentative working concept of the neurophysiological mechanisms which influence the electroencephalogram may be summarized as follows. In the relaxed waking state, spontaneous cortical electrical activity is dominated by the intrinsic activity of groups of cortical neurones. Excitation, whether arising from stimuli within the organism, or in peripheral receptors, tends to produce two opposed effects: (i) synchronization of cortical electrical activity through impulses in thalamic relay nuclei and "upward" hypothalamic pathways; (ii) compensatory (?) desynchronization of cortical electrical activity through activitation of diencephalic and midbrain reticular inhibitory mechanisms which act on medial and anterior thalamic nuclei, and also through "downward" discharges from sympathetic centers in the hypothalamus which produce vasoconstriction via the cervical sympathetic chains. Under conditions which promote somnolence, cortical electrical activity tends to exhibit periodic hypersynchrony which is due partly to functional "isolation" of cerebral cortex and

partly to impulses to the cortex from medial, and possibly anterior thalamic nuclei whose activity is "released" from inhibitory control by reduction in activity of the diencephalic and midbrain reticular mechanisms. Any or all of the mechanisms which tend to synchronize cortical electrical activity may be involved in the production of the extreme hypersynchrony which characterizes cortical electrical "seizure" discharges. Within this framework, the neurophysiologic mechanisms which regulate spontaneous cortical electrical activity, and their bearing on the interpretation of the effects of drugs on the electroencephalogram may be considered in some detail.

a. Intrinsic spontaneous electrical activity of cerebral cortex. Libet and Gerard (210) demonstrated that isolated frog olfactory bulb exhibits regular rhythmic electrical activity which can be modified by electric stimulation and changes in osmotic pressure, electrolyte concentrations, pH and temperature. Curiously, abolition of synaptic conduction by nicotine did not alter rhythmic activity. In another report (209) these investigators observed that electrical disturbances can also be transmitted without synaptic conduction since "caffeine waves" were propagated across brain tissue which had been severed and then reapposed. Kristiansen and Courtois (197) reported that in the cat, cerebral cortex which had been completely isolated except for its blood supply displayed rhythmic electrical activity which appeared in "bursts" of 8 to 12 cycles per second rhythms, and reacted to electrical stimulation and topical application of physostigmine and acetylcholine in a manner similar to that of intact cerebral cortex. In contrast to these observations, Burns (56) found that in cats anesthetized with chloralose all spontaneous cortical electrical activity disappeared in a block of cerebral corex which had been isolated similarly. In man, Echlin, Arnett and Zoll (102) demonstrated that complete neuronal isolation of cerebral cortex caused a marked depression of spontaneous cortical activity but low voltage rhythmic activity similar to that of the surrounding brain persisted. After 20 to 50 minutes, spontaneous bursts of high voltage rhythmic activity began to appear in the isolated cortex.

In these experiments, the spontaneous activity of isolated cerebral cortex resembled the electroencephalographic patterns which occur during certain stages of sleep in intact human subjects (Davis and coworkers, 70) or in animals, rather than the alpha rhythms of man. If only corticothalamic connections are severed, as in frontal lobotomy in man, alpha activity is not abolished and "burst" activity (analogous to "sleep spindles") do not occur as long as the subject is awake (Lennox and Coolidge, 206; Henry, 161). Other clinical evidence (Brazier, 37); Hayne, Belinson and Gibbs, 152; Hoagland, 169) also indicates that in part, the electroencephalogram is dependent on intrinsic rhythmic activity of groups of cortical neurons. Also in the cerebral cortex, "suppressor" mechanisms may modify such activity, apparently through cortico-caudato-thalamocortical circuits (Dusser de Barenne and coworkers, 97, 98). McCulloch, Graf and Magoun (248) have shown that one of these "suppressor" areas in the cortex (4-s) is functionally integrated with bulbar inhibitory centers. However, Sloan and Jasper (314), Essig and Marshall (110) and Marshall, Hanna and

Barnard (230) believe that, insofar as their effects on the electroencephalogram are concerned, the "suppressor" mechanisms are identical with the "spreading depression" phenomenon which may be a non-specific effect produced by trauma, dehydration or other adventitious disturbances. In the cortex also, seizure activity may be propagated through cortico-cortical connections in short neuron chains and long commissural fibers (McCulloch, 246).

It seems possible therefore, that the progressive slowing of cortical rhythms which occur after repeated doses of analgesics (Andrews, 13) or other agents is due in part to direct cortical action. Likewise, the bilaterally asynchronous discharges produced by the analgesic drugs (morphine, methadone) appear to be due partially to direct cortical effects (Wikler and Altschul, 362).

The differences between the effects of the volatile and the non-volatile anesthetics may perhaps be explained on the work of Swank and Watson (326). These investigators concluded that amobarbital depresses first the smaller neurones (low voltage, faster activity) and later the large neurones (higher voltage, slower activity), whereas ether has reverse effects. This hypothesis is analogous to that of Heinbecker and Bartley (155) concerning the action of these agents on peripheral nerve fibers of different size. However, in cats, Reinberger and Jasper (273) found that the patterns of spontaneous cortical electrical activity were poorly correlated with cerebral cytoarchitecture.

The transitory increase in frequency and voltage produced by agents which subsequently slow rhythmic activity, notably the barbiturates, has been explained in various ways. Hoagland (quoted by Brazier and Finesinger, 38) suggested that such fast activity may be due to accumulation of acid metabolites in cortical cells. Toman and Davis (332) thought that increased synchronization of previously asynchronous low voltage fast activity brought about by prolongation of recovery time in cortex and thalamus could account for this phenomenon. On the other hand, the work of Sugar and Gerard on anoxia (324) indicates the possibility that increased frequency and voltage of cortical rhythms after depressant drugs might be due to transitory excitation on the way to depression.

Cortical after-discharge consequent to electrical stimulation appears to be based on neural activity which is independent of that responsible for spontaneous activity since mephenesin depresses cortical after-discharge without altering spontaneous electrical activity (Kaada, 186).

b. Thalamo-cortical circuits. The spontaneous activity of cerebral cortex may be modified greatly by activity in the thalamus. In cats anesthetized with pentobarbital, electrical stimulation of the medial group of thalamic nuclei produces "recruiting" responses which appear diffusely in the cortex and which are identical in frequency and rhythmicity with the spontaneous cortical electrical activity (Dempsey and Morison, 84; Morison and Dempsey, 254). In unanesthetized cats, stimulation of medial thalamic nuclei evokes diffuse bilaterally synchronous spike or spike and dome discharges which are similar to those seen in patients suffering from "grand mal" or "petit mal" epilepsy (Hunter and Jasper, 175). The difference between the observations of these two groups of

investigators may be due to differences in the intensity of excitation of neurons in the medial thalamic nuclei consequent to electrical stimulation under different experimental conditions. In the unanesthetized cat, electrical stimulation of the fornix and anterior thalamic nuclei produces changes in behavior and in the electroencephalogram which resemble those seen in human subjects during attacks of "psychomotor" epilepsy (Hunter, 174). The ventrolateral and ventral posterolateral nuclei of the thalamus, as well as the geniculate bodies are relay stations for different sensory pathways to the cerebral cortex. Electrical stimulation of these structures evokes responses which are localized in the cortical projection areas of the particular group of activated thalamic neurons. Morison, Dempsey and Morison (252) and Dempsey and Morison (83) observed that such evoked "primary" responses in the cortex were highly localized and showed no tendency to repetitive activity. However, Dusser de Barenne and McCulloch, (96) and Chang (63) have presented evidence which indicates that sensory impulses set up not only localized "primary" responses but also localized "secondary" repetitive responses in the cortex which are maintained by reverberating circuits between the cortical projection area and the corresponding thalamic sensory relay nuclei. Forbes and Morison (117) and Morison, Dempsey and Morison (253) also described "secondary" repetitive cortical responses to afferent stimulation which, however, were diffuse. The relationship between these "secondary" diffuse responses to afferent stimulation and the "recruiting" responses which are evoked by stimulation of medial thalamic nuclei is not clear.

Because of the similarity in pattern between the bilaterally synchronous seizure discharges in the electroencephalogram which are produced by large amounts of the analgesic drugs (morphine and methadone in animals; meperidine and ketobemidone in man), and those evoked by stimulation of medial thalamic nuclei, it be may be inferred that such drug effects are due to apparent stimulation of this thalamic region.

Both "primary" and "secondary" cortical responses to sensory stimulation are suppressed by ether (Derbyshire and coworkers, 86). Barbiturates do not suppress the "primary" response. The "secondary" response is not wholly suppressed but the rhythmic electrical discharges corresponding to it may be fewer due to elevation of threshold of neurons in thalamus and cortex which subserve such activity (Forbes and Morison, 117). Marshall (229) has shown that the recovery time of the ventrolateral nucleus pars externa of the thalamus is prolonged. Mephenesin does not affect the primary response but depresses the secondary response even though it does not alter spontaneous activity in the thalamus or cortex (Kaada, 186).

c. Basal Reticular and Hypothalamic Mechanism. Recent evidence indicates that the thalamic mechanisms already discussed may be influenced by regulating mechanisms in the reticular substance of the diencephalon and midbrain, and also in the hypothalamus. Moruzzi and Magoun (256) have shown that in cats lightly anesthetized with pentobarbital, stimulation of the reticular substance in the diencephalon and midbrain produces signs of arousal and desynchronization of the electroencephalogram, apparently through an inhibitory effect on the

activity of medial thalamic nuclei. That such mechanisms are activated by sensory impulses is suggested by the observations of Dempsey, Morison and Morison (82) who described a "third" response in the cerebral cortex after stimulation of peripheral nerve. This response consisted of "suppression" of spontaneous cortical electrical activity and the impulses which evoked it were mediated through midline structures in the midbrain. Conversely, in the cat, lesions in the basal reticular substance produce somnolence and synchronization of the electroencephalogram (Lindsley, Bowen and Magoun, 212), apparently through "release" of activity in medial thalamic nuclei. The resulting electroencephalographic pattern resembles strikingly that which occurs in natural sleep or in moderately deep barbiturate anesthesia. Murphy and Gellhorn (257) have shown that stimulation of the hypothalamus increases the frequency and amplitude of cortical rhythms and this effect is enhanced by section of the cervical sympathetic chains. Darrow and co-workers (75–78) reported that increased sympathetic activity is associated with cerebral vasoconstriction and tends to slow the electroencephalogram, thus acting as part of a self-regulating homeostatic mechanism. Lesions in the hypothalamus reduce spontaneous cortical electrical activity (Obrador, 262).

Since analgesic doses of morphine or methadone do not produce "sleep patterns" in the human electroencephalogram, it may be inferred that the clinical effects of these drugs are not related to depressant actions on the hypothalamus or the diencephalic and midbrain reticular mechanisms. However, repeated doses, of morphine may affect the electroencephalogram indirectly through actions on the hypothalamus. This is suggested by the observation of Andrews (10) who found that in subjects actively addicted to morphine, the alpha percentage was surprisingly high, and the demonstration by Himmelsbach (163) that the sympathetic nervous system become hyperirritable during morphine addiction. These two observations may be related since Darrow (*loc. cit.*) has shown that high alpha percentage is associated with cerebral vasoconstriction consequent to heightened sympathetic tone.

The ease with which "sleep patterns" in the electroencephalogram are induced in human subjects by ordinary hypnotic doses of barbiturates indicates that such drugs have powerful actions on hypothalamic and basal reticular regulating mechanisms. Grinker (139) and Grinker and Serota (140) found that barbiturates produced slow activity in the hypothalamus (sphenoid lead) of the cat, but Hoagland and coworkers (170) found no changes in the electrical activity of the supra-optic and mammillary body regions in the hypothalamus.

II. DIENCEPHALON

1. Morphine and methadone

a. Effects on reflex responses. In dogs that had survived 18 months after ablation of all neocortex and portions of archicortex, Wikler (351) observed that subcutaneous injection of morphine in doses as small as 5 mg./kg. or of 3 mg./kg. of methadone reduced greatly the skeletal motor components of "sham rage" evoked by a variety of methods, such as pinching the footpads, compression of

the tail, electrical stimulation of the skin, restraint, or handling. These components included struggling, biting, snapping, vocalization, clawing and lashing of the tail. Vocalization was somewhat less affected than the other components of "sham rage". In addition, lowering of body temperature, slowing of the pulse and respiration, loss of righting reflexes, and a state of somnolence from which the dog could be partially aroused were induced. Thresholds of muscle twitch of the lower lip (in response to electrical stimulation of a canine tooth with bipolar electrodes through double amalgam fillings) were elevated. Larger doses of morphine (up to 250 mg./kg.) produced greater effects of the same kind and the duration of effects was greatly prolonged (up to 2 days after the largest doses). Convulsive twitches (but not well developed seizures) and occasional spontaneous running movements, rise in temperature and tachycardia were observed four to eight hours after the largest doses. After small or large doses of these drugs the startle reflex was enhanced and the corneal and wink reflexes were not affected. Effects on muscle tone were variable. With smaller doses, extensor rigidity of the forelegs and exaggerated positive supporting reactions in these limbs occurred at times, but flaccidity was noted frequently. These observations are in agreement with the findings of Mettler and Culler (250) who found that the narcotic effects of morphine were greatly intensified in dogs after decortication. However, Amsler (8) reported that the analgetic effects of morphine disappeared after removal of the cerebral cortex in rats, guinea pigs, rabbits and dogs. The reasons for these divergent observations are not apparent, although the possibility exists that differences in the amount of archicortex removed by these investigators may account for the differences observed in relation to the analgetic actions of morphine, since there is increasing evidence that such structures play an important role in the integration of emotional mimetic reactions (Fulton, 120).

In acute and chronic decorticated cats, Wikler (344, 329, 347) found that intravenous or subcutaneous injection of morphine 5 mg./kg. abolished the skeletal motor components of "sham rage" and the righting responses initially. Extensor rigidity of the forelegs was prominent after morphine. One or two hours following injection, spontaneous locomotor movements appeared which could be inhibited by nociceptive stimulation, such as pinching the tail. Concomitantly, the startle response was enhanced while the wink and corneal reflexes were unaltered. It was also observed that, as in the intact cat, the pupils were dilated after morphine and this effect was not altered by section of the cervical sympathetics. In the "hypothalamic" animal (thalamus and basal ganglia largely removed), the depressant effects of morphine on "sham rage" were somewhat less pronounced and motor restlessness appeared earlier. Hambourger (142) also reported that morphine produces delayed motor restlessness in decorticated cats. In some experiments he was able to demonstrate that localized hypothalamic lesions abolished the delayed excitant action of morphine in such preparations. However, Brooks, Goodwin and Willard (42) were unable to abolish delayed restlessness after morphine by hypothalamic lesions.

In both intact and decorticated cats with adrenals ligated or removed, and

anesthetized with urethane, morphine (5 to 10 mg./kg. intravenously) reduced the magnitude of the responses of the nictitating membrane to electrical stimulation of the sciatic nerve (Wikler, 343). This was observed also in some preparations in which there was a slight spontaneous contraction of the nictitating membrane after morphine. In contrast, morphine did not exert any appreciable effect on blood pressure responses to the same stimulus. In unanesthetized decorticated cats immobilized with dihydro-beta-erythroidine or "Intocostrin", the effects of morphine were more difficult to evaluate. These curarizing agents appeared to block partially the responses of the nictitating membrane before morphine, and yet no change in responses of the nictitating membrane was consistently observed after morphine in such experiments. A possible central morphine-curare antagonism may account for this, since it has been reported that curare exerts stimulating effects on the central nervous system while blocking conduction in sympathetic ganglia and skeletal myoneural junctions (Eccles, 101; McCawley, 242, 243, Cohnberg, 68).

b. Direct effects. Masserman (235) studied the effects of morphine on the "sham rage" responses of intact cats evoked by direct electrical stimulation of the hypothalamus through implanted bipolar electrodes. The effects on the skeletal motor responses were observed in unanesthetized recovery preparations and those on the autonomic components of "sham rage" (blood pressure and respiration) in cats under light ether anesthesia. Local hypothalamic injection of 1 to 10 mg. of morphine sulfate (total dose) or intraperitoneal administration of 30 to 100 mg. of morphine (total dose) did not affect the reactivity of the hypothalamus except that, in animals which received more than 60 mg. intraperitoneally, the hypothalamic responses were limited to the duration of the stimulus. However, in urethanized cats, Wikler (346) found that the responses of the nictitating membrane to direct bipolar electrical stimulation of the hypothalamus were reduced by morphine, although much less so than the reflex response to sciatic stimulation.

Co Tui, de Bodo and Benaglia have demonstrated that morphine hyperglycemia in the cat is dependent on the integrity of the sympathetic innervation in the adrenal glands (70). Bodo and Brooks (35) also showed that morphine hyperglycemia was abolished by transection of the spinal cord at the sixth cervical segment, indicating that morphine exerts its hyperglycemic effect by an action on supraspinal structures. In further investigations, Brooks, Goodwin and Willard (42) found that morphine hyperglycemia was abolished by massive lesions in the posterior hypothalamus of cats.

The antidiuretic action of morphine in the dog was studied by de Bodo (34). Morphine 2.5 to 5 mg./kg. produced a marked retention of tap water given either. by stomach tube or intravenously. The same effect was observed in adrenal-inactivated dogs and in dogs in which the adenohypophysis had been removed. However, no antidiuretic effect of morphine could be demonstrated in dogs in which the neurophypophysis was removed. This investigator noted that like pitressin, morphine inhibits water, but not saline diuresis, and increases excretion of urinary chlorides. Morphine, however, does not potentiate the antidiuretic

action of pitressin. The author concludes that morphine antidiuresis is produced by a stimulant action on the hypothalamus, resulting in increased production of antidiuretic hormone. Since acetylcholine acts similarly, he suggested the possibility that reduction of cholinesterase activity by morphine produced this effect. On the basis of data obtained from study of renal hemodynamic changes produced by morphine in normal dogs and in hypophysectomized dogs with diabetes insipidus, (Handley and Keller, 144) concluded that in addition to an effect on the hypothalamus, morphine may produce antidiuresis by a direct action on nephrons. Isbell (178) has confirmed the fact that morphine produces antidiuresis in man, and that this is also true for methadone. However, in man, both pitressin and morphine inhibit saline diuresis partially, and reduce urinary excretion of chlorides.

In dogs, Hemingway (156) found that 10 mg./kg. of morphine causes immediate shivering with rise in skin temperature followed by a fall, and rise in rectal temperature when the ears begin to cool. The excess of heat is dissipated partly by panting which may set in before shivering ceases. Panting threshold to rise in skin or rectal temperatures was lowered. This was observed in panting which occurred both spontaneously after morphine alone and after addition of diathermy. Under morphine, panting could occur even when the rectal and skin temperatures had been reduced and without raising these temperatures to the normal threshold range. The author infers that morphine sensitizes the anterior hypothalamus both to direct heat and to impulses arising from a heated skin. This conclusion is supported by recent evidence which shows that in the monkey sweating and polypnea are produced by stimulation of the pre-optic region of the hypothalamus (Beacon and coworkers, 23).

2. Other drugs

a. Effects on reflex actions. Mettler and Culler (250) have observed that a variety of anesthetic agents exert more profound narcotic actions on decorticated dogs than in normal dogs. Wikler (343) has observed similar effects of pentobarbital on decorticated cats. Wikler and Frank (360) observed that after electroshock convulsions in chronic decorticated cats righting and licking reflexes returned rapidly (half to one hour) as did the skeletal motor components of "sham rage" induced by handling, whereas the same pattern in response to nociceptive stimulation did not return for two to four hours after the convulsions.

b. Direct effects. Masserman (232) observed that intravenous or intraperitoneal injection of 20 to 50 mg./kg. of sodium amobarbital diminished or abolished the sympathetic and emotional mimetic reactions of the hypothalamus to faradic stimulation. Direct injection of minute amounts of the drug into the hypothalamus produced depression of respiration and fall in blood pressure but little change in reactivity. De Bodo and Prescott (36) found that phenobarbital consistently, and amobarbital or pentobarbital inconsistently, exerted antidiuretic effects in normal dogs which was less than that observed after analgesic doses of morphine, even when the barbiturates were given in full anesthetic doses. When

antidiuresis occurred it appeared to have been produced by the same mechanisms as after morphine, since it persisted after removal of the adenohypophysis, disappeared after removal of the neurohypophysis and water excretion was much more affected than that of saline. Richter (275) reported that, as in normal sleep, administration of amobarbital, somnifene, chloral or paraldehyde markedly elevated skin resistance in the cat's footpads and concluded that these drugs depress or inhibit sympathetic activity originating in the hypothalamus. That skin resistance is regulated primarily by the hypothalamus is also suggested by the observation of Forbes and Andrews (116) which indicate that, in man, the alpha rhythm of the cortex and the psychogalvanic response are controlled independently. Laidlaw and Kennard (207) studied the state of the capillaries in the central nervous system following the administration of different anesthetics by injection of India ink and gelatin into the vascular system. In barbiturate anesthesia numerous dilated capillaries were seen in the supra-optic and paraventricular nuclei of the hypothalamus. In ether anesthesia relatively few capillaries were open and these were constricted. In contrast, the capillaries of the cortex were more dilated by ether than by barbiturates. The authors concluded that this evidence points to a hypothalamic site of action of barbiturates.

Masserman (236, 240) has reported that in cats, the threshold of the hypothalamus to direct faradic stimulation is lowered after direct injection of minute amounts of 0.01 per cent alcohol, but is raised after injection of larger amounts. Intraperitoneal injections of alcohol had no effect on the threshold of the hypothalamus to direct faradic stimulation. This author also noted (232) that ether anesthesia did not alter the reactivity of the hypothalamus to direct stimulation. Masserman (233) further reported that intraperitoneal administration of 0.14 to 0.16 mg./kg. of strychnine sulfate did not consistently lower the threshold or increase the intensity of the reactions of the animal to faradic stimulation of the hypothalamus although it caused hyperesthesia and increased emotional irritability. Direct injections of metrazol and picrotoxin into the hypothalamus (Masserman, 237) produced "sham rage" and this procedure as well as intravenous injection or intraperitoneal administration of these drugs increased the reactivity of the hypothalamus to direct faradic stimulation.

3. Comparison of effects of morphine with those of other drugs

Although some minor exceptions do exist, it appears to be true that in general, barbiturates depress responses of the hypothalamus both to direct and reflex stimulation. Morphine depresses only the responses to reflex excitation, while the analeptic drugs enhance both types of responses. Of particular interest are the dual effects of morphine and methadone. Depressive actions of these drugs are indicated by the reduction of "sham rage" responses to reflex stimulation and the narcosis induced by morphine or methadone in decorticated dogs. Excitant actions of morphine or methadone are indicated by the antidiuretic effect, the hyperglycemic action, the sensitization of the heat-dissipating center and, perhaps, the delayed motor restlessness induced by these drugs in decorticated cats.

4. Neurophysiologic mechanisms of drug action

Since morphine does not affect the "sham rage" pattern when this is evoked by direct electrical stimulation of the hypothalamus, its depressant action on "sham rage" evoked by reflex stimulation must be attributed to an action on afferent impulses impinging on hypothalamic structures. A prominent feature of most of the components of "sham rage" is their long duration after cessation of the stimulus, when "sham rage" is evoked by reflex stimulation. It may, therefore, be inferred that morphine reduces reflex after-discharge in the hypothalamus by a depressant action on reverberating chains of internuncial neurones in the afferent arm of the reflex response. This inference in supported by the contrasting effects on the responses of the nictitating membrane and blood pressure of the decorticated cat under urethane anesthesia. As noted above, morphine reduces the magnitude of the nictitating membrane reflex response, but not that of the blood pressure. Rosenblueth and Schwartz (280) have shown that the nictitating membrane reflex response to afferent nerve stimulation is characterized by a prominent after-discharge. Bronk, Pitts and Larrabee (40, 269) have demonstrated that after-discharge is not present in sympathetic nerves subserving blood pressure and other cardiovascular responses to either reflex stimulation of afferent nerves or to direct stimulation of the hypothalamus. The hypnotic effect of morphine in decorticated animals may perhaps be attributed to a reduction in afferent internuncial bombardment of structures in the hypothalamic "waking" or "activating" centers (Moruzzi and Magoun, 256), or to a direct depressant effect on the latter. Aside from such a direct depressant action, the direct effects of morphine on the hypothalamus appear to be excitant (hyperglycemic and antidiuretic effects, sensitization of the heat loss mechanism). Whether the depressant and excitant actions of morphine are due respectively to stimulation or depression of inhibitors, or conversely to depression and stimulation of facilitators, cannot be decided on the basis of available evidence. It does appear that one apparently depressive effect, lowering of body temperature, may in part be due to "stimulation" of the heat-loss center in the hypothalamus. Theoretically, similar mechanisms may account for other depressive effects, such as the action of morphine on reflex responses of the nictitating membrane, since Morison and Rioch (251) have shown that these responses can be inhibited by stimulation of the anterior hypothalamus. These questions can be answered only by further experimentation.

In contrast to the absence of demonstrable direct depressant effects of morphine on the hypothalamus, the barbiturates exert a powerful direct depressant action on this structure. The only "stimulant" action of barbiturates on the hypothalamus which has been demonstrated thus far is the occasional antidiuretic effect of some members of this class of drugs. It may therefore be concluded that, in addition to depression of afferent internuncial activity (see below), barbiturates—unlike morphine—also depress "motoneurones" within the hypothalamus. Similar patterns of action of these two types of drugs are noted in other parts of the nervous system (see below).

III. BRAIN STEM

1. Morphine

In acute decerebrated cats, Wikler (344) found that 5 to 15 mg./kg. of morphine had small and variable effects on the extensor rigidity of these preparations. Intravenous injection usually enhanced extensor tone and sometimes induced an extensor seizure. The labyrinthine reflexes were not affected but, after morphine, tonic neck reflexes were less easy to demonstrate. In some preparations after the larger doses of morphine, rhythmic alternating movements of the forelegs appeared half to one hour after injection, concomitantly with progressive increase in the "startle" reaction to sudden striking of the table on which the animals rested. These rhythmic movements could be readily inhibited by exteroceptive stimuli, such as touching, pinching, or pressure on the footpads. Such stimulation also produced apnea or slowing of respiration. Conversely, when exteroceptive stimuli were reduced by suspending the preparation off the table, rhythmic running movements increased in rapidity. In a few cases, such activity was noted even before injection, but was then greatly augmented by morphine. This phenomenon appeared to be dependent on the exact plane of intercollicular section, but the latter was not demarcated precisely.

In a decerebrated dog which survived 7 weeks after completion of transection of the midbrain, Wikler (343) observed that after subcutaneous injection of 2 to 25 mg./kg. of morphine, extensor rigidity was markedly reduced in the hindlimbs, but only slightly in the forelimbs. Tonic neck reflexes could still be elicited in the forelimbs after morphine. Slowing of cardiac rate was not observed after morphine and the higher doses of the drug produced tachycardia. Pilomotor and skeletal motor responses in the lower lip were elicited by electrical stimulation of a canine tooth with bipolar electrodes applied to double amalgam fillings; the thresholds of these reactions were elevated by all doses of morphine used.

Marshall and Rosenfeld (228) observed that in cats and dogs anesthetized with sodium phenobarbital and also injected with morphine, oxygen reduced respiratory minute volume and this effect was abolished by denervation of the sino-aortic mechanisms. This was explained on the basis that, after morphine, respiration is largely maintained by sino-aortic chemoreceptor reflex mechanisms for which anoxemia is the adequate stimulus. Schmidt (289) found that morphine reduced the sensitivity of the respiratory center to CO_2 but enhanced the sensitivity of the carotid body to cyanide. Similar effects of morphine on the respiratory center and chemoreceptor activity were reported by Dripps and Dumke (93). Dripps and Comroe (94) observed in man that maximal depression of respiration occurred three to seven minutes after intravenous injection of morphine and was not greater than that observed after intramuscular injection.

Henderson and Rice (157) found that, in urethanized rabbits, 3 to 5 mg./kg. of morphine slowed respiratory rate and frequently reduced tidal volume. Concomitantly, all vagal respiratory reflexes were enhanced; *i.e.*, morphine enhanced the respiratory accelerating effects of continuous low frequency (10 to 20 per sec.) stimulation of the proximal end of the severed vagus nerve, the accelerat-

ing effects of high frequency (50 to 75 per second) stimulation during inspiration and the slowing effect of high frequency stimulation during expiration. These investigators concluded that, since such effects are also noted under conditions of lowered alveolar CO_2, the similar effects of morphine could be explained on the basis of lowered CO_2 in the respiratory center and reflex arcs, even though the drug produces a rise in alveolar CO_2 concentration, or lowered sensitivity of the central mechanisms to CO_2. These observers also found that morphine increased the augmentation of rate, volume and ventilation of respiration produced by stimulation of sensory nerves, such as the posterior tibial and the great auricular. These findings are in contrast to the results of earlier studies by Maloney and Tatum (226) who found that, in urethanized rabbits, morphine depressed respiratory responses to sciatic nerve stimulation.

Enhancement of the carotid sinus pressure reflex by morphine in man has been observed by Rovenstine and Cullen (281). Marri and Hauss (227) have reported that morphine enhances respiratory reflexes in response to stimulation of pressoreceptors in the carotid sinus.

The effect of morphine in slowing of the heart was attributed to direct vagal stimulation by Robbins, Fitzhugh and Baxter (278) since morphine bradycardia persisted after intercollicular section. They demonstrated that ligation of the carotids or ether anesthesia may mask this effect because of tachycardia produced by these procedures. These authors felt that the findings of McCrea and Meek (245), which indicated that morphine bradycardia was due to cortical depression with "release" of vagal tone, were incorrect because these earlier experiments had been performed under ether anesthesia and after ligation of the carotids. However, Allen, Murphy and Meek have presented other data in which such complicating factors were eliminated, and which indicate that morphine does not stimulate the medullary vagal center directly (4).

Henderson and Graham (158) reported that in acutely decorticated dogs the pupils were only about 1.0 mm. smaller than in the normal dog and that morphine produced a marked miosis in the decorticated animals. Injury of the corpora quadrigemina caused marked pupillary dilatation, and morphine then failed to produce miosis. McCrea, Eadie and Morgan (244) found that, in both dog and man with optic nerves intact, the degree of morphine miosis varied with the light intensity falling on the retina. In dogs with one optic nerve cut, morphine miosis varied in degree with changes in light intensity falling on the contralateral retina. The authors inferred that morphine accentuates the normal light reflex. Depression of sympathetic activity is probably not a factor in morphine miosis in dogs since Amsler (quoted by McCrea, Eadie and Morgan, 244) found that section of the cervical sympathetics did not reduce the degree of pupillary constriction produced by this drug.

Drew, Dripps and Comroe (92) observed that, while intramuscular injection of 10 to 30 mg. of morphine in man produced no statistically significant changes in pulse rate, blood pressure or cardiac output, sudden tilting from the previously horizontal to the upright position resulted in fainting or evidences of impending circulatory collapse in 44 per cent of the subjects. This effect could not be attrib-

uted to depression of the cardio-accelerator mechanisms since, after morphine, the immediate response to tilting was increased cardiac acceleration. The Hering-Breuer respiratory reflexes also appeared to be enhanced. The authors concluded that vasomotor collapse on tilting after-morphine was due to a peripheral vasodilating action of the drug similar to that produced by nitrites or histamine. These findings contribute also to an explanation of the increase in side reactions after morphine which is more prominent in ambulatory patients than in bed patients (Comroe and Dripps, 69). Huggins, Handley and La Forge (173) found that, in the dog, elevation of the hind legs or head to a 45 degree angle resulted in a significant reduction of blood flow to the part raised. They suggested that morphine may produce a partial inhibition of the vasoconstrictor center. However, a peripheral vasodilating effect of morphine may also explain these observations.

2. Other drugs

In contrast with the effects of morphine, mephenesin reduces or abolishes the extensor rigidity of decerebrated cats (Henneman and Scherer, 160; Henneman, Kaplan and Unna, 159; Kaada, 186). Henneman, Kaplan and Unna (159) observed that mephenesin reduces the facilitating effects on the kneejerk which are produced by stimulation of the corresponding brain stem reticular inhibiting and facilitating systems described by Magoun and Rhines (223, 224). Kaada (186) reported similar results and noted that, whereas mephenesin in doses of 25 to 60 mg./kg. was required to depress the effects of brain stem reticular stimulation, only 10 to 20 mg./kg. of mephenesin were sufficient to depress the inhibiting effects of cerebellar stimulation on the kneejerk. In man, mephenesin exerts sedative effects (Schlan and Unna, 288) in addition to actions on postural mechanisms (Stephen and Chandy, 323).

Marshall and Rosenfeld (228) observed that, in contrast to morphine, administration of chlorbutanol, urethane, paraldehyde or alcohol did not result in respiratory depression by oxygen in the dog. Schmidt (289) reported that, like morphine, chloralose enhanced the sensitivity of the carotid body chemoreceptors to cyanide; ether had opposite effects and the effects of barbital were variable. Dripps and Dumke (93) found that unlike morphine, ether and cyclopropane depressed chemoreceptor sensitivity to cyanide. Barbital, pentobarbital and thiopental either did not affect chemoreceptor sensitivity or enhanced it.

Henderson and Rice (157) reported that the effects of ether on the respiratory center and vagal reflexes were opposite to those of morphine. Ether increased respiratory rate, volume and ventilation, yet depressed or abolished vagal reflexes. These investigators concluded that ether increases the sensitivity of the respiratory center to CO_2. Whitteridge and Bülbring (369), on the basis of observations on electrical activity in single pulmonary afferent vagal fibers, concluded that all volatile anesthetics caused an increase in the sensitivity of stretch receptors in the lung. Cyclopropane and nitrous oxide exerted such effects throughout exposure. Ethyl chloride, chloroform, ether and trichlorethylene first stimulated and then depressed the stretch receptors. In contrast to mor-

phine, Marri and Hauss found that barbital and "evipal" depressed respiratory reflexes from pressoreceptors in the carotid sinus (227).

In the decerebrated as well as in the normal cat, Gellhorn and Darrow (131) observed that metrazol convulsions were accompanied by intense stimulation of both sympathetic and parasympathetic autonomic systems. Following convulsions, or in the absence of convulsions (after repeated small doses of metrazol with curare), increased reflex excitability of the sympathetic system was demonstrated by lowering of the threshold and the increased responses of the nictitating membrane, blood pressure, the normally innervated pupil and sweating in the footpads on afferent stimulations.

3. Comparison of effects of morphine with those of other drugs

Few depressant actions of morphine on the skeletal motor reactions of the decerebrated animal have been reported, in contrast to the marked effects on extensor rigidity which are produced by myanesin. The delayed excitatory locomotor effects produced by morphine in some decerebrated preparations have not been reported for other drugs. Whereas barbiturates, as well as morphine, depress respiration, augmentation of respiratory reflex responses to stimuli from chemoreceptors and stretch receptors in the carotid sinus and lungs is much more pronounced after morphine. Ether appears to have quite opposite effects to those of morphine. While there is general agreement on the enhancement by morphine of stretch reflexes involving the respiratory center, there are conflicting reports on the effects of this drug on respiratory reflexes induced by stimulation of cutaneous sensory nerves. Metrazol appears to enhance autonomic activity both directly and in response to afferent stimulation.

4. Neurophysiologic Mechanisms

Since morphine induces locomotor activity in some decerebrated cats, the motor restlessness which is observed after morphine, methadone or similar agents may be due to an action of these drugs in the midbrain. Bailey and Davis (19) have described a syndrome of obstinate progression in the cat which was produced by a localized lesion in the region of the interpeduncular region of the midbrain. The similarity of the results of such lesions and the locomotor activity induced in the decerebrated cat by morphine suggest an action of the drug on the interpeduncular nucleus or on inhibitory or facilitatory mechanisms controlling it. Since morphine affects decerebrate rigidity but little, it maybe inferred that it has little effect on the brain-stem reticular mechanisms described by Magoun and Rhines (223, 224) and by Sprague and coworkers (322). However, a specific study of the effects of morphine on this system has not yet been done. It is evident that morphine enhances reflex respiratory responses to afferent vagal stimuli by a central action, and this is probably true for the reflex respiratory and vasopressor responses to stimulation of chemoreceptors and stretch receptors in the lung and carotid sinuses. The neuronal characteristics of such reflexes are not well known but, from inspection of records in the literature, it appears that after-discharge is not prominent. The absence of depressive effects of mor-

phine on such responses may be another example of specific action of morphine on after-discharge. The enhancement of such reflexes by morphine is more difficult to explain since, concomitantly, the responsiveness of the respiratory center to CO_2 is depressed. In addition to loci of action of the drug in the brain stem, cerebellar effects may also play a role, since Moruzzi (255) has demonstrated that stimulation of the paleocerebellum inhibits respiratory and vasopressor responses to stimulation of chemoreceptors and carotid sinus stretch receptors. The mechanisms of action of morphine on the pupil in various species remains obscure. The differences in neural innervation of the pupil in relation to afferent stimulation in different species make analysis of data difficult. The importance of oculomotor inhibition in the pupillary reaction of the cat to afferent stimulation has been pointed out by Ury and Gellhorn (335), Seybold and Moore (302) and Kuntz and Richins (201). Furthermore, Harris, Hodes and Magoun (150) have demonstrated that the afferent pathways from periphery to midbrain, which subserve reflex pupillary dilatation, are distinct and separate from the spinothalamic tracts. However, Weinstein and Bender (342) have shown that, whereas parasympathetic inhibition plays the major role in reflex dilatation of the pupil in the cat, sympathetic stimulation is the more important feature in the monkey. Other factors, as yet unknown, must also contribute to the differences in pupillary reaction to morphine in various species, since the drug causes dilatation of the pupil in both cat and monkey (Seevers, 282) and miosis in dog and man.

IV. SPINAL CORD

1. Morphine and methadone

De Bodo and Brooks (35) observed that in the chronic spinal cat, morphine abolished the flexor, crossed extensor and Philippson's reflexes, and depressed slightly the kneejerk, especially its clonic features, when the latter were present. In acute and chronic spinal cats, Wikler (344) noted that, whereas the flexor, crossed extensor and Phillippson's reflexes were depressed by morphine, the kneejerk was enhanced or unchanged after intravenous or subcutaneous injection of 5 mg./kg. of the drug. Analogous results were obtained in acute spinal cats by studying, in cut ventral roots, the action potentials evoked by stimulation of afferent nerves from muscle, cutaneous sensory nerves or dorsal roots (Wikler, 330). After intravenous injection of 5 mg./kg. of morphine the action potentials in two-neuron arcs were enhanced or unaffected, whereas the potentials in multineuron arcs were reduced. After intravenous injection of 15 mg./kg. of morphine action potentials in two-neuron arcs were reduced, while voltages of potentials in multineuron arcs underwent biphasic changes—reduction followed by enhancement. Leimdorfer (204) found that neither morphine nor methadone produced significant changes in the electrospinogram of cats, although occasional bursts of small waves were noted after large doses of morphine. After large doses of methadone, spike seizure discharges appeared in the electrocorticogram but no change was observed in the electrospinogram. He concluded

that the convulsant effects of methadone, and probably of morphine as well, were cortical, not spinal in origin.

Wikler and Frank (361) studied the effects of morphine and methadone in long-surviving chronic spinal dogs, using an isotonic recording apparatus. The effects of the drugs were similar. The ipsilateral extensor thrust was enhanced, the kneejerk was slightly and variably affected, while the flexor, crossed extensor, Philippson's and stepping reflexes were markedly reduced or abolished. Doses of 5 to 50 mg./kg. of morphine and 2 to 10 mg./kg of methadone were used. Little change in effects on reflexes was noted, except for prolongation of effects, until convulsive doses were employed (150 mg./kg. of morphine or 40 mg./kg. of methadone). Such doses produced tonic or tonic-clonic seizures which were limited to the portion of the body rostral to the spinal cord transsection. These authors are therefore in agreement with the conclusions of Leimdorfer (*loc. cit.*) regarding the locus of origin of the seizures produced by large doses of morphine or methadone.

Houde and coworkers (171) studied the effects of 5 and 10 mg./kg. morphine, 3, 5 and 10 mg./kg. of methadone and 50 mg./kg. of meperidine on the tail flick response to radiant heat stimuli in albino rats before and after transection of the spinal cord between D-5 and D-8 segments. They found that this response was essentially the same in the intact and in the spinal preparation, and that the drugs used prolonged the reaction time of the reflex before and after transsection of the spinal cord, although for any given dose the depressant effects were less marked in the spinal animal. These investigators also noted that the cutaneous maximus twitch in response to radiant heat applied to the skin of the back was elicitable in dogs whose spinal cord had been transected between C-5 and C-6 segments, and that the reaction thresholds of this reflex were elevated by intravenous injection of morphine in doses of 2 and 10 mg./kg.

Houde and Wikler (172) investigated further the segmental characteristics of the cutaneous maximus twitch in the dog. They found that the afferent arm of the reflex arc extended from about D-2 to L-5 segments, while the efferent arm was sharply localized to C-8 segment and ventral roots from this region innervated the fan-shaped cutaneous maximus muscle through the external thoracic nerve. In chronic spinal dogs whose spinal cord had been transected or hemisected above C-8 segment, the reflex was readily obtainable on stimulation of the skin with radiant heat or pinching with a toothed forceps. There was no significant difference in the cutaneous maximus reflex in dogs before and after transection, or on the two sides after hemisection, although, in some, the reflex was somewhat enhanced by cord section. Morphine, methadone or meperidine depressed the cutaneous maximus responses in the spinal animal, though not to the same degree as in the intact animal. The authors conclude, therefore, that measurement of analgesic potency by the methods of D'Amour and Smith (73), Andrews and Workman (17), Ercoli and Lewis (108), etc. is, at least in part, a measurement of the depressant effects of drugs on a spinal reflex, and that the reliability of these methods in evaluating analgesic potency rests on positive correlations between the results of data so obtained and clinical observations.

2. Other drugs

Beecher, McDonough and Forbes (25) reported that in cats under ether anesthesia, long-sustained contractions of flexor muscles, recorded isotonically or isometrically, were obtained by stimulation of the popliteal or sciatic nerves by repetitive break-shock stimuli. In contrast, under "Evipal", responses were larger but much less sustained. They noted that this barbiturate produced changes in the flexor reflex which were similar to that produced by transection of the spinal cord (Forbes, Cobb and Catell, 118). Wikler (348) noted that, in the acute spinal cat, intravenous injection of pentobarbital reduced the amplitude of both two-neuron and multineuron arc discharges in ventral roots which were evoked by stimulation of gastrocnemius muscle afferent or cutaneous sensory nerves. With large doses of pentobarbital, both types of response were abolished. In acute spinal cats breathing progressively increasing concentrations of ether, the multineuron arc discharges were reduced first but, later, both two- and multineuron arc discharges were reduced and finally abolished. Knoefel (189) observed that, in the acute spinal cat, various derivatives of barbituric and thiobarbituric acids either depressed or enhanced the flexor reflex, depending on the dose. He noted that phenomena of central nervous stimulation may be produced in the intact animal by compounds which are purely depressant to the spinal flexor reflex. Henneman, Kaplan and Unna (159) found that mephenesin has no effect on the normal kneejerk (monosynaptic reflex arc) but depresses the flexor and crossed extensor reflexes (multisynaptic reflex arcs). Mephenesin also reduced the inhibition of the kneejerk produced by stimulation of the ipsilateral sciatic nerve, but the depression of this inhibitory system was less marked than the effects produced by mephenesin on brain stem inhibitory and facilitatory systems. On the other hand, mephenesin appeared to depress "spontaneous" inhibition and facilitation in the spinal cat, since the kneejerks were "regularized" after injection of the drug. Kaada (186) also described the effects of mephenesin on spinal reflexes. In the spinal cat, up to 40 mg./kg. of mephenesin had no effect on monosynaptic or multisynaptic discharges over ventral roots, but doses of 40 to 60 mg./kg. depressed the multisynaptic discharges, leaving the monosynaptic discharges unaffected. Enhancement of multisynaptic discharges by 0.1 to 0.15 mg./kg. of strychnine was abolished by 25 to 60 mg./kg. of mephenesin. Similar results were obtained in the study of the kneejerk, flexor and crossed extensor reflexes with myographic technics. Neostigmine, 10 to 50 mg./kg. intravenously, enhanced the kneejerk, and the ipsilateral flexor reflex. The effects of neostigmine were abolished by mephenesin. Berger (30) had reviewed the literature on spinal cord depressant drugs. He points out that glyketal and benzimidazole possess properties which are qualitatively the same as those of mephenesin. However, glyketal (29, 30), which exerts the most marked depressant effect on multineuron arc reflexes, possesses the weakest antistrychnine action. Benzimidazole depresses the multineuron reflexes less, yet has the most powerful antistrychnine action, while mephenesin possesses both properties to a marked degree. Parpanit resembles all these agents in its action on multineuron spinal reflexes, but differs from them in that it does not produce paralysis. Schweitzer

and Wright (294) found that physostigmine enhanced the kneejerk of the spinal cat but neostigmine depressed it, as did intravenous injection of acetylcholine. Merlis and Lawson (249) found that, in the spinal dog, physostigmine depressed the kneejerk and enhanced the flexor and crossed extensor reflexes. Bülbring and Burn (55) were able to separate central effects of drugs from peripheral actions by perfusing the spinal cord and hindlimbs separately in the cat. These investigators found that both physostigmine and neostigmine depressed the kneejerk and augmented the flexor reflex. In acute spinal cats, Wikler (348) noted that intravenous injection of physostigmine enhanced the two-neuron reflex arc discharges over ventral roots, but had little effect on multineuron arcs. However, in previously morphinized spinal cats, physostigmine enhanced multineuron arc discharges. In chronic spinal dogs, Wikler and Frank (361) noted that both physostigmine and neostigmine enhanced all spinal reflexes and physostigmine produced rhythmic or nonrhythmic spontaneous movements of the hindlimbs. These effects were abolished by intravenous injection of morphine or methadone. Calma and Wright (61) found that physostigmine injected intrathecally in spinal cats enhanced the kneejerk, had inconstant effects on the flexor reflex, prolonged the crossed extensor reflex and evoked a "jar" reflex. Jacobsen and Kennard (185) reported that hindlimb reflexes in the chronic spinal monkey during the state of "spinal shock" could be restored permanently by one or more injections of ephedrine.

3. Comparison of effects of morphine with those of other drugs

Wikler and Houde (363) compared the effects of morphine, methadone, thiopental, pentobarbital, mephenesin and benzimidazole on the hindlimb reflexes of chronic spinal dogs. They found that the patterns of reflex change produced by these drugs could be divided into three groups: (1) Morphine and methadone enhanced the ipsilateral extensor thrust, slightly depressed or enhanced the kneejerk, and markedly depressed the flexor, crossed extensor and Philippson's reflexes; (2) Thiopental and pentobarbital progressively depressed all reflexes; (3) Mephenesin and benzimidazole enhanced the kneejerk, or did not affect it, and reduced the flexor, crossed extensor and Philippson's reflexes, as well as the ipsilateral extensor thrust. In each case, the depressed reflexes recovered in an order inverse to that in which they were depressed, *i.e.*, Philippson's and crossed extensor reflexes were reduced earlier and recovered later than the flexor reflex. Morphine and methadone were the only drugs in the series studied which enhanced the ipsilateral extensor thrust. The authors suggested that a study of the pattern of effects of a new compound on the hindlimb reflexes of chronic spinal dogs may be useful in determining whether the agent under investigation is likely to possess general properties similar to the opiate analgesics, barbiturate anesthetics, or mephenesin-like paralytic drugs.

4. Neurophysiologic mechanisms

The demonstration by Renshaw (274) and Lloyd (216–219) that the spinal stretch reflex is mediated over a two-neuron, or monosynaptic pathway, while

cutaneous reflexes are mediated over multineuron, or multisynaptic reflexes, has increased to a great extent our understanding of the neural mechanisms involved in the action of drugs on the nervous system. It is evident that drugs resembling morphine, barbiturates or mephenesin in their actions all possess in common the ability to depress multineuron arc discharges whose after-discharge is mediated by activity in reverberating interneuron chains (Bernhard, 31). Interneurons have therefore been considered to be the site of action of barbiturates (Beecher, McDonough and Forbes, 25: Barany, 20; Bremer, 39), morphine (Wikler, 344) and mephenesin (Henneman, Kaplan and Unna, 159; Kaada, 186, Berger, 30). The differences between the actions of these agents on other reflexes in the spinal animal must therefore be attributed to differences in their actions on motoneurons and on inhibitory and facilitatory mechanisms.

Data already presented indicate that the barbiturates depress the reflex excitability of motoneurons as well as internuncials. Brooks and Eccles (43, 45–48) have demonstrated that the essential event which normally inaugurates motoneuron discharge is the development of a "synaptic" potential in the immediate vicinity of the motoneuron by the arrival of impulses in the terminal endings of presynaptic fibers. The motoneuron soma is depolarized when this "synaptic potential" reaches a critical level. Brooks and Eccles (44) have concluded that "The anesthetic pentobarbital, though depressing the activity of all components of the monosynaptic pathway, produces a block in transmission essentially by stabilizing the motoneuron membrane so that the synaptic potential no longer initiates the discharge of impulses." The effects of morphine or mephenesin on the motoneuron have not been investigated with the technics employed by Brooks and Eccles. However, the fact that most observers have reported that mephenesin does not alter the uninhibited or unfacilitated two-neuron arc indicates that this drug does not affect motoneurons except in very large doses (Kaada, 186). In "analgesic" doses, morphine appears not to affect motoneurons, but may have a direct or indirect excitant effect on them, since the ipsilateral extensor thrust is regularly enhanced in chronic spinal dogs by this drug. It is noteworthy that this reflex, although probably transmitted over a three-neuron arc (Lloyd, 219), is characterized by the absence of after-discharge (Sherrington, 303).

Further light on some of the differences between the actions of morphine, barbiturates or mephenesin-like drugs may be shed by investigations of the actions of these drugs on spinal inhibitory and facilitatory systems. Two types of inhibition have been described in the nervous system. One is the reduction in effectiveness of a previously adequate afferent stimulus to produce motoneuron discharge because of antecedent subliminal stimuli delivered within a critical time interval. This has been ascribed to refractoriness in internuncial neurons due to preceding activity induced by the first, or "conditioning" stimulus, and is termed "indirect" inhibition. The other is the inhibition of the two-neuron arc discharge which is effected by impulses arriving from antagonistic muscles or through antagonistic reflexes, and those effects are exerted directly on the motoneuron (Lloyd, 214, 215, 220; Brooks and Eccles, 45–47). This is termed "direct" inhibition, and may be prolonged by internuncial activity (Lloyd, 221). Similarly,

both "indirect" and "direct" facilitation hav been described (Erlanger and Gasser, 109; Lloyd, 220). Of the groups of drugs under consideration, only mephenesin has been investigated with regard to actions on such inhibitory or facilitatory systems. Henneman, Kaplan and Unna (159) have presented evidence which indicates that mephenesin reduces such inhibitory activity as is mediated through internuncial neurons but not that which is exerted on the motoneuron by impulses arriving in its vicinity directly.

A point of interest with regard to the neural basis of spinal action of drugs is to what extent such interpretations may be transferred to other parts of the nervous system. That this is not a simple problem is indicated by the fact that Szentagothai (328), using histological degenerative technics, was unable to find evidences of monosynaptic pathways rostral to the spinal cord except in certain trigeminal reflexes.

As noted in previous sections, some of the actions of morphine have been attributed to its ability to inhibit cholinesterase activity. The evidence relating to action on the spinal cord is somewhat contradictory, and the drawing of parallelisms between the actions of morphine and those of other cholinesterase inhibitors or acetylcholine would not be justified.

V. PERIPHERAL NERVE

Although morphine is not a local anesthetic, actions on peripheral sense organs or nerves after systemic administration of the drug cannot be excluded on this basis alone. No work during the past decade on such possible actions has come to the attention of the reviewer. However, local anesthetic actions of methadone have been reported by Chen (67) and Everett (111). This problem deserves further study.

Section Two. Tolerence and Physical Dependence

I. SPECIES DIFFERENCES

Whereas tolerance to and physical dependence on morphine have been demonstrated repeatedly in man, chimpanzee (Spragg, 321), monkey (Seevers, 297, 298), dog (Pierce and Plant, 267), rabbit (Cahen, 57; Ko, 191) and rat (Himmelsbach, Gerlach and Stanton, 167), divergent results have been reported by different observers in studies of the newer synthetic analgesic agents. Tolerance and physical dependence to methadone have been reported in man by Isbell and coworkers (180). On withdrawal of this drug after a period of addiction, definite evidence of physical dependence was observed, but this was slower in onset, less intense and more prolonged than that produced by morphine addiction. In a preliminary report, Scott and Chen (295) observed no tolerance to the analgetic effect of methadone in daily doses up to 2 mg./kg. in dogs. However, in a subsequent study, Scott and coworkers (296) were able to demonstrate tolerance to the analgetic and narcotic actions of this drug in dogs receiving daily injections for as long as 56 days. No tolerance was developed to the actions of methadone in slowing the heart rate or increasing intestinal motility. The only signs of physical

dependence to methadone which were observed by these investigators were tachycardia and low-grade fever during the first two days of withdrawal. Finnegan and coworkers (114) found little evidence of tolerance to the depressant effects of methadone in dogs. On the other hand, Wikler and Frank (361) observed definite evidence of tolerance to the analgetic and narcotic effects of methadone in dogs when the drug was injected subcutaneously every six hours for several weeks. On abrupt withdrawal of the drug, most dogs exhibited severe abstinence signs which consisted of tremors, twitches, restlessness, aversion to man, vomiting, hydrophilia, tachycardia, fever and rhinorrhea. These signs appeared within 10 hours after the last injection, reached a peak within 24 hours and gradually subsided during the next few days. In monkeys, Seevers (299) found no evidence of tolerance to methadone when injections were made once daily, but tolerance did develop on repeated daily injections. However, physical dependence to methadone was not demonstrated in this species. Isbell (177) reported that tolerance developed to the pain-threshold raising action of keto-bemidone in man, and that on abrupt withdrawal an extremely intense morphine-like abstinence syndrome developed which was more severe, and appeared sooner after the last injection than that after morphine addiction. Lewis (208) observed that tolerance to the analgesic effect of keto-bemidone did develop in dogs, but abstinence symptoms on abrupt withdrawal of the drug were mild.

The reasons for such species differences are unknown. From the evidence, it appears that route and frequency of injections do influence the development of tolerance, and perhaps to a certain extent, physical dependence (as in dogs). However, other factors such as differences in metabolism and excretion of the drugs may play a role.

II. LOCI OF ORIGIN

A. The cerebral cortex

1. Frontal lobotomy In recent years, a number of reports of the incidental effects of frontal lobotomy on drug addiction have appeared. While all reports are in general agreement regarding the absence of craving for morphine after this procedure in patients addicted to opiate or similarly acting drugs, there is disagreement with reference to the presence or absence of withdrawal signs. Unfortunately, no controlled observations have been reported in which the intensity of withdrawal signs have been measured before and after frontal lobotomy. Also, in several reports, morphine was withdrawn by what is equivalent to a rapid reduction after the operation or the patient was not examined for withdrawal signs until several days to a week after discontinuing the drug. The reports are therefore difficult to evaluate. Scarff (285), Mason and Hamby (231), and Koskoff and coworkers (195) have reported that addicted patients showed no withdrawal signs on discontinuation of the drugs after frontal lobotomy. On the other hand, Watts and Freeman (341), Dynes and Poppen (99) and Hamilton and Hayes (143) reported definite evidence of withdrawal signs in their patients. The report of Hamilton and Hayes (*loc. cit.*) is the most clear-cut. Of 13 addicted patients upon whom they performed frontal lobotomy for the relief of pain, nine showed

withdrawal signs, three did not, and one died. The signs of withdrawal included tremor, sweating and diarrhea which lasted four or five days if untreated. Single injections of morphine abolished these signs, which appeared in less intense form after the effects of the drug wore off. These signs of abstinence were present even though lobotomy was successful in relieving pain.

A controlled study of the effects of bilateral frontal lobotomy on the morphine abstinence syndrome has been made by Wikler, Pescor, Kalbaugh and Angelucci (364) on two patients with schizophrenia of long standing, in whom the operation was required for therapeutic reasons. After a period of control observations, subcutaneous injections of morphine were given in gradually increasing doses until the patients were stabilized on 60 mg. of the drug every 6 hours. They were then observed hourly after abrupt withdrawal of morphine for a period of 42 hours, after which the previous dose schedule was resumed. Two weeks later, bilateral frontal lobotomies were performed on each patient, morphine injections having been discontinued just before the operation. During the next 42 hours the patients were again observed hourly. Before frontal lobotomy, abrupt withdrawal of morphine was followed by the appearance of yawning, lacrimation, rhinorrhea, mydriasis, elevation of body temperature, lassitude, anorexia and vomiting in one patient, and yawning, lacrimation, rhinorrhea, gooseflesh, elevation of blood pressure, muscle twitches, anorexia and vomiting in the other. After frontal lobotomy, abrupt withdrawal of morphine was followed by the appearance of the same signs in each patient, though the severity of the abstinence signs was reduced and anorexia and vomiting were altogether lacking. Both before and after frontal lobotomy, subcutaneous injection of the stabilization dose of morphine caused a prompt subsidence of the abstinence signs. Neither before nor after frontal lobotomy did either of the patients display any interest in or recognition of the drug, nor did they ask for or indicate that they enjoyed the effects of the injections.

From these observations it may be concluded that in man the frontal lobe is involved in the genesis of the morphine abstinence syndrome, along with other parts of the nervous system. In particular, frontal lobotomy reduces suffering, craving and purposive behavior directed toward obtaining opiate-like drugs, which are inportant features of the morphine abstinence syndrome clinically. Separation of the anterior portions of the frontal lobe from the rest of the nervous system also produces an attenuation of the nonpurposive morphine withdrawal signs. This is to be expected since it has been shown that important autonomic regulatory centers are located in various portions of the frontal lobe in man and the higher animal species (Fulton, 120). Although other parts of the frontal lobe contribute to autonomic regulation (Bucy and Pribram, 54), such functions are particularly prominent in the orbital and cingular gyri (Smith, 315, 316; Bailey and Sweet, 18; Kremer, 196; Delgado and Livingston, 81). The orbital gyri in the monkey also subserve regulation of motor activity and appetite (Ruch and Shenkin, 282). In the usual operative procedure, radiations to the thalamus from the medial and *anterior* orbital portions of the frontal lobe are interrupted, but the cingular gyrus is spared (Scarff, 286).

2. The electroencephalogram During morphine addiction, Andrews (13) noted definite evidence of tolerance to the presumably cortical effects of the drug. During abstinence, he observed that the alpha percentage remained high, in spite of suffering of the subjects and the appearance of marked autonomic signs. He inferred therefore, that the withdrawal signs were subcortical in origin, and suggested that the hypothalamus was the most likely locus of origin. Isbell and coworkers (180) noted that variable degrees of tolerance were developed to the effects of methadone on the electroencephalogram of man. In those subjects in whom tolerance was poorly developed, slow activity in the electroencephalograms persisted for 4 or 5 days after withdrawal. This suggests a persistence of direct effects of methadone for a relatively long time after withdrawal and may account for the mildness of the abstinence syndrome in these subjects. Altschul and Wikler (6) studied the electroencephalograms of subjects during a cycle of addiction to keto-bemidone. Tolerance to the effects of the drug on the electroencephalogram developed readily. During the severe abstinence syndrome which ensued after abrupt withdrawal of the drug, slow activity reappeared. They noted that this coincided more or less with the "yen sleep" which is a feature of morphine-like withdrawal syndromes. In the course of studies on the electroencephalographic changes during meperidine addiction in man, Andrews (11) observed that during abstinence, the electroencephalogram returned to the normal control pattern sooner than the tremors, which appeared during addiction, subsided. He inferred that the tremors are subcortical in origin on the basis of this evidence as well as the fact that the frequencies of the grosser tremors had no representation in the electroencephalogram.

B. Diencephalon

In long-surviving chronic decorticated dogs, Wikler (350, 351) observed the development of tolerance to the depressant effects of morphine or methadone on "sham rage", elevation of tooth pain reaction thresholds, and body temperature. On abrupt withdrawal of either drug, the preparations exhibited a well marked abstinence syndrome which could be divided into five stages: (a) an initial stage of restlessness and irritability which was a continuation of the usual pre-injection behavior; (b) quiescence, but further increase in irritability, during which yawning, rhinorrhea, salivation, fever, vomiting and peculiar postures appeared; (c) a second period of restlessness during which irritability steadily diminished; (d) sniffing, rooting and gnawing at the floor of the tub in which the animals were kept, associated with almost complete absence of "sham rage" responses; (e) gradual cessation of such behavior with return to posture and activity similar to that present before addiction. During stages (b) to (d) inclusive, a single injection of morphine temporarily abolished the abstinence signs, increased irritability and restored the animals posture and behavior to a more "normal" level. It is noteworthy that such an injection of morphine or methadone produced effects during abstinence which were directly opposite to those produced by these drugs before addiction or after recovery from abstinence. This indicates that a biological need for the drugs was present during the abstinence period. Serial sections

were made of the remaining brains in the two decorticated dogs upon whom the most complete studies were made (Wikler, 352). These showed complete removal of neocortex and partial removal of olfactory cortex, pyriform lobe, corpus striatum, hippocampus and thalamus. This investigator concluded that in the dog the abstinence signs after withdrawal of morphine or methadone were, in part at least, subcortical in origin. However, he pointed out that in man cortical effects may play an important role in the genesis of the abstinence syndrome since there is evidence for telencephalization of autonomic function in the higher species (Spiegel, Miller and Oppenheimer, 320; Smith, 316).

C. Spinal Cord

Wikler and Frank (361) observed that, in chronic spinal dogs, tolerance developed to the depressant effects of morphine or methadone on the hindlimb reflexes (flexor, crossed extensor and Philippson's responses) but not to the excitant action on the ipsilateral extensor thrust. After abrupt withdrawal of either drug, a well defined abstinence syndrome developed in the hindlimbs which was qualitatively similar after either morphine or methadone addiction, but appeared earlier and subsided sooner in the latter case. In general, the reflexes which had been depressed by these drugs in the non-tolerant animal (flexor, crossed extensor and Philippson's responses) became hyperactive, while the extensor thrust and kneejerks were markedly reduced or abolished. In addition, spontaneous rhythmic alternating movements of the hindlimbs appeared at the peak of the abstinence syndrome which occurred 24–30 hours after methadone withdrawal and 72–90 hours after morphine withdrawal. The hindlimb abstinence syndrome subsided about three days after methadone withdrawal and five days after morphine withdrawal. During the height of abstinence, a single injection of morphine or methadone temporarily reduced the abstinence changes in the hindlimbs. These observers concluded that the spinal cord is involved directly or indirectly in the morphine or methadone abstinence syndrome of the dog. In unmedicated "normal" chronic spinal dogs, hyperthermia produced no appreciable effects on the hindlimb reflexes. Other indirect factors, however, were not eliminated as possible sources for the hind limb abstinence changes. These included humoral agents and afferent sensory impulses from viscera, some of which could have reached the spinal cord below the level of transection.

Indirect effects of humoral agents on the spinal cord must be considered since Bender and Kennard (28) have observed that, in the monkey, the induction of fright by various methods results in twitches of completely denervated facial muscles. Since the usual signs of morphine or methadone abstinence, including whining, restlessness, etc., in the dog are observed in the portion of the animal's body rostral to the spinal transection, it is possible that a humoral agent, presumably cholinergic in nature, is released during this period and affects the spinal cord caudal to the transection by way of the blood stream.

Indirect effects of afferent impulses from viscera must be considered since Dusser de Barenne and Ward (95) have shown that, in the monkey, distension of the bladder produces changes in hindlimb reflex activity which is in the same

direction as that noted during abstinence as described above, namely, inhibition of the kneejerk and augmentation of the flexor reflex. However, the time course of the hindlimb reflex changes during abstinence from methadone or morphine was more prolonged than that of the changes noted in the animal rostral to the level of spinal cord transection (D 10–12) and there was little prolonged disturbance of bowel or bladder activity during the period. Wikler and Frank also pointed out that the use of chronic spinal dogs may facilitate studies on addiction liability of drugs although such preparations may give exaggerated pictures of abstinence due to sensitization of the cord to chemical agents below transection by "deafferentation" (Drake and Stavraky, 89).

D. Skeletal muscle

Shideman and Seevers (304–306) have reported that the oxygen uptake per milligram dry weight per hour of minced hindlimb skeletal muscle of the chronically morphinized rat was definitely higher than that of normal muscle. Oxygen uptake rose gradually in such preparations, reached a peak at 48 hours and gradually subsided over a period of six days. They noted that the time course of the changes in oxygen uptake was similar to that of the morphine withdrawal syndrome. However, addition of morphine to the minced rat skeletal muscle during this period increased oxygen uptake as in normal muscle. It should be noted that this effect is opposite to that of morphine on the central nervous system during abstinence, since during this time injection of the drug reduces the abstinence signs.

E. Other organs and organisms

Abood (1) reported that, in the brains, livers and kidneys of rats, single subcutaneous injections of 50 mg./kg. of morphine increased the rate of glycolysis from glucose 50 per cent, and repeated daily subcutaneous injections of up to 250 mg./kg. of morphine caused a similar increase up to 65 per cent. In skeletal muscle, increased rate of glycolysis was observed only in those rats which were given daily injections of morphine. Cahen (58) has reported that tolerance to the effects of morphine can be demonstrated in the isolated frog's heart. Yo (379) observed tolerance to heroin in the hay-amoeba. The development of tolerance and physical dependence to morphine in tissue cultures was reported by Sasaki (318) and by Kubo (199). Kubo (200) also observed that isolated chick embryo iris epithelium develops tolerance to the deleterious effects of morphine on its growth; when it is transferred to media not containing morphine or other drugs, growth is again impaired.

III. MECHANISMS OF TOLERANCE

A. Urinary excretion of morphine

The problem of the role played by changes in metabolism and urinary excretion of morphine has been reopened for investigation by the discovery of a "bound" form of morphine in the urine of dogs by Gross and Thompson (141), and of man

(Oberst, 260). These observers found that morphine is excreted in the urine in three forms: free morphine, easily hydrolyzable morphine and difficultly hydrolyzable morphine. Thompson and Gross (331) found that non-tolerant and tolerant dogs excrete about 20 per cent of an injected dose of morphine in the "free" form. Non-tolerant dogs excrete 8 per cent of an injected dose of morphine in the "easily hydrolyzable" and 66 per cent in the "difficulty hydrolyzable" forms, leaving only 6 per cent unaccounted for. Tolerant dogs excrete about 16 per cent of an injected dose of morphine in the "easily hydrolyzable" and 29 per cent in the "difficulty hydrolyzable" forms, leaving 35 per cent unaccounted for. Therefore the possibility exists that the tolerant dog is able to destroy or otherwise inactivate morphine to a much greater extent than the non-tolerant animal.

B. Vascular tolerance

Schmidt and Livingston (290) demonstrated the fact that tolerance to the vasodilating action of morphine can be developed in dogs and cats after the removal of all nervous system influences, indicating that such tolerance is due to the development of resistance to the effects of the drug within the vascular cells. Shideman and Johnson (307) compared the development of tolerance and cross-tolerance to the acute vascular effects of morphine, meperidine and methadone. They found that, in the anesthetized dog, intravenous injection of morphine, meperidine, or methadone results in an acute fall in blood pressure with gradual recovery occurring over a variable period of time. Repeated injection of morphine results in complete vascular tolerance. Only partial acute tolerance develops to meperidine. After successive injections of methadone, little change was noted in the acute lowering of blood pressure, but recovery was more prompt, indicating tolerance to the prolonged hypotensive effects of intravenous injection of this drug. Repeated injection of meperidine produces no tolerance to morphine or to the acute hypotensive effects of methadone. Repeated administration of methadone results in no cross-tolerance to morphine or meperidine. The authors believed that anesthesia interferes with the compensatory mechanisms involved in the development of acute tolerance.

C. Anti-morphine substances

The synthesis of N-allylnormorphine and the demonstration by Unna (334) and Hart and McCawley (151) of antagonistic effects of this compound on the sedation and analgesia produced by morphine in animals suggest that older theories of tolerance based on presumptive production of anti-morphine substances in the body merit further investigation.

D. Periodicity of tolerance

Goetzl, Burrill and Ivy (137) reported that tolerance developed to the analgesic actions of morphine as measured by their adaptation of the method of Koll and Reffert (193), but the degree of tolerance fluctuated periodically. However, this may be due in part to erratic variations in the threshold-raising action of morphine, for Altschul and Wikler (7), using a similar method, have observed that in

the non-tolerant dog, the elevation of tooth-pain reaction threshold varies markedly after administration of morphine or methadone at irregular intervals of one to two weeks over a period of several months.

E. Residual Tolerance

On the basis of the minimal and variable "pain-threshold" elevations after injection of morphine observed by him in post-addicts, Andrews inferred that such subjects possess a degree of residual tolerance as a result of previous addictions. However, as noted in other sections of this review, Isbell found that morphine exerted variable effects on "pain-threshold" in non-addicts as well as post-addicts and that the changes produced by the drug were comparable in the two groups. Andrews (10) also noted that the distribution curve of alpha percentages in the electroencephalograms of 50 post-addicts differed from norms in the literature in that extremely high (90 to 100 per cent) and extremely low (0 to 10 per cent) alpha percentages were more common in post-addicts, and concluded that some irreversible changes had been produced in the cortical electrical activity of post-addicts as a result of previous use of the drug. However, Wikler and Ruble (365), in a comparative study of electroencephalograms of non-addicts, marihauna users and post-addicts, found that, when the subjects were matched for age, no significant differences in alpha percentage distributions were found. Although the ages of Andrews' subjects are not known, it is possible that the inclusion of a large group of subjects in the 20 to 30 year age range may have been responsible for the high incidence of subjects with very high alpha percentages since it is well known that the highest alpha percentages are found in normal subjects in that age range (Gibbs and Gibbs, 134).

Himmelsbach (166) also observed that resting blood flow in the hand was lower in post-addicts than in normal subjects and inferred that, in post-addicts, the sympathetic nervous system was somewhat hyperactive as a result of previous addictions to morphine. However, heightened sympathetic "tone" in post-addicts may be related to personality characteristics which anteceded experience with morphine, since the personalities of most post-addicts is by no means "normal" (Felix, 107).

IV. MECHANISMS OF PHYSICAL DEPENDENCE

A. Psychogenic factors

The publication of some reports describing absence of withdrawal signs in addicted subjects following frontal lobotomy (see above) has given rise to renewed interest in the role of psychogenic factors in the genesis of the opiate abstinence syndrome (105). Mason and Hamby (231) concluded that withdrawal signs are psychogenic because they did not observe these changes after abrupt withdrawal of narcotics coincident with the performance of frontal lobotomy on a paraplegic patient. Aside from the fact that other observers have noted withdrawal signs in addicted patients after frontal lobotomy, the conclusions of Mason and Hamby are unwarranted since the presence or absence of abstinence phenomena following brain operations can permit inferences concerning only the loci of

origin of these changes, not their etiology. Nevertheless, it is true that experienced observers have often been unable to evaluate the "psychogenicity" or "organicity" of the opiate abstinence syndrome. The signs and symptoms exhibited during withdrawal in themselves give no clue regarding their origin since the autonomic nervous system in particular can respond only in stereotyped ways to stimuli, whether these be neural impulses evoked in response to emotional disturbances or to cellular chemical changes (Wikler, 345). However, several lines of evidence indicating that non-psychogenic factors are at least partly responsible for the abstinence syndrome may be summarized. (1) The order of appearance of some of the abstinence signs such as rhinorrhea, lacrimation, yawning and gooseflesh is different from the signs of emotionally produced anxiety. (2) The intensity of the morphine abstinence syndrome in post-addicts is related in a predictable way to the dose level during morphine addiction (Andrews and Himmesbach, 16). (3) Successful hypnosis, as indicated by the appearance of suggested anesthesia, paralysis somnambulism and post-hypnotic suggestion, fails to affect the abstinence signs during the first 36 hours of withdrawal; beyond that period, hypnosis cannot be induced successfully because of the subject's intense discomfort (Vogel, 337). (4) The time course and intensity of the abstinence syndrome vary considerably and predictably after addiction to various drugs such as morphine, methadone and keto-bemidone. (5) Physical dependence to morphine and other drugs has been demonstrated in intact animals. (6) Physical dependence has been demonstrated to morphine and methadone in chronic decorticated dogs. In these preparations, "psychogenic factors" (*i.e.*, factors of symbolic significance) are reduced to a minimum, since extensive studies on these animals (Wikler, 352) have indicated that they were unable to develop conditional responses to visual, auditory or time stimuli; tactile conditional motor responses were produced after prolonged conditioning, but these could be explained on the basis of spinal facilitation of the flexor reflex such as that described by Porter and Taylor (270). Physical dependence to morphine and methadone has also been observed in chronic spinal dogs. (7) During the morphine abstinence syndrome in man high percentage alpha activity may continue in the electroencephalogram (Andrews, 10). In purely emotional anxiety states, alpha activity is largely replaced by low voltage fast activity. (8) Withdrawal signs have been noted in newborn infants of mothers addicted to opiates (Perlstein, 265). (9) Changes suggestive of physical dependence have been observed in isolated organs or tissue cultures.

However, such evidence does not exclude the participation of psychogenic factors in the modification of the opiate abstinence syndrome. The reaction of the subject to his discomfort and to the meaning of withdrawal of drugs certainly contributes to the total picture of abstinence, both in regard to subjective symptoms and objective signs. Wikler (351) has suggested that the central nervous system effects of morphine, including the changes responsible for the abstinence syndrome, may become conditioned to meaningful stimuli and in this way contribute not only to its intensity but also to the motivation for relapse. Further experimentation is needed for the validation of the hypothesis. Lindesmith (211)

believes that the efficacy of morphine in relieving suffering during the withdrawal period plays an important role in the motivation for relapse in addicts.

B. Homeostatic mechanisms

Because of the general similarity between the signs of hyperthyroidism and those of the opiate abstinence syndrome, Sakel (283) advanced an hypothesis of cellular (neuronal) adaptation in the central autonomic nervous system on the model of Ehrlich's side-chain theory. He suggested that such cells possess receptors which are able to link with either morphine or circulating hormones. During addiction to morphine, the side-chains which normally accept hormone molecules are linked to morphine molecules. In adaptation to this, new side-chains are developed by the autonomic nerve cells, and these are again linked to morphine as the dosage is increased. On abrupt withdrawal, the increased number of side-chains are set free concomitant with the excretion or destruction of morphine, and are able to be linked with great amounts of circulating hormone which excite the autonomic cells and so produce the autonomic discharges which characterize the abstinence syndrome. No experimental data were offered in support of this hypothesis.

Himmelsbach (165) has advanced a theory of physical dependence based on presumptive homeostatic adaptations of the autonomic nervous system in support of which some experimental evidence is available. He has summarized this hypothesis as follows: "(1) The prime function of autonomic (hypothalamic) centers is to maintain homeostasis and to make proper adjustments in the face of stress. (2) Morphine affects homeostasis through its action on these centers. (3) Autonomic reaction to this effect takes place..... (4) With repetition, the ability to offset the opiate effect improves (physiologic tolerance). (5) An extension of this process of improved reaction results eventually (with larger and more frequent doses) in disproportionate strength in checks and balances. (6) Thus a condition is created wherein a chemical is needed to maintain homeostasis; such reactive power having been developed that, to preserve equilibrium, there must be present an effect to counteract. (7) Since the body is unable to supply a counter-effect promptly it must be furnished from without, else equilibrium will be lost temporarily. Such loss of equilibrium results in an abstinence syndrome. Following subsidence of this spectacular illness, as much as six months of total abstinence may be required to regain optimum steady states." (See also Himmelsbach, 164). Some other observations by Himmelsbach tend to support this hypothesis. Thus, he observed (166) that, in a patient with a unilateral dorsal sympathectomy, morphine produced an increased blood flow to the hand with intact sympathetic innervation, but not in the sympathectomized hand; local cooling and heating altered blood flow comparably in either hand. He therefore inferred that morphine depresses the sympathetic nervous system. From evidence which has been reviewed in other sections, it would appear that such an effect could be ascribed to afferent internuncial but not to efferent "motoneuron" portions of the autonomic nervous system. Himmelsbach (163) observed further that, in individuals actively addicted to morphine, the vasopressor response to a standard cold stim-

ulus was greater and recovery after removal of the stimulus was slower than in normal subjects. This observation points to a hyperirritability of the autonomic nervous system during maintained addiction to opiates.

The assumption of direct depressant effects of opiates on the autonomic nervous system is, however, not essential for theories of physical dependence based on homeostatic autonomic reactions, for Gellhorn (129) has shown that excitation of the autonomic nervous system is a regular reaction to stresses (anoxia, asphyxia, hypoglycemia, hypercapnia) which depress activity in the somatic nervous system.

Another type of autonomic homeostatic response during addiction to and withdrawal of opiates is suggested by the work of Shideman and Seevers (305, 306) and Shideman (304). These investigators suggested that morphine causes an increase in the metabolism of skeletal muscle, the effects of which are masked by central depressant effects; the effects of morphine on skeletal muscle persists for some time after depressant effects of the drug have worn off, and may be responsible directly or indirectly for abstinence signs. It is possible, therefore, that the autonomic signs which appear during abstinence may represent increased activity in the autonomic nervous system in response to the increased metabolic requirements of skeletal muscle.

The increased autonomic activity during the withdrawal period in opiate addiction is explained in another way by an hypothesis advanced by Pfeiffer and coworkers (266). These investigators stated that the *l*-methadone abstinence syndrome was less intense than that of heroin and that the difference may be related to their observations that whereas *l*-methadone raises the threshold of both "supain" and "sympain", heroin raises the threshold of "supain" and does not affect that of "sympain". During heroin addiction, "sympain" thresholds may be lowered continually, so that during abstinence, autonomic reactions to "sympain" stimulation may appear, whereas this is less marked after addiction to methadone. However, on the basis of this hypothesis, one would expect that the dilaudid abstinence syndrome should be relatively mild, since Pfeiffer and coworkers (*loc. cit.*) have shown that this drug elevates "sympain" thresholds considerably. Yet King, Himmelsbach and Sanders (188) have reported that in man a relatively prompt and intense, though short-lasting abstinence syndrome follows withdrawal of dilaudid.

C. Dual effects of morphine on the central nervous system

The well known theory of Tatum, Seevers and Collins (330) postulates that opiates simultaneously depress some functions of the nervous system and excite others; the excitant effects outlast the depressant effects and become manifest as withdrawal signs during abstinence. From evidence which has already been presented in this review, it is evident that there are numerous examples of such dual actions of opiates and similarly acting compounds. However, during addiction cycles to morphine and methadone in chronic spinal dogs, the excitant action of morphine on the extensor thrust disappears during the withdrawal period, whereas those reflexes which were previously depressed by the drugs become hyperactive (Wikler, 361). As noted above, this suggests local cellular adaptation to

depressant effects of the drug within the central nervous system rather than a persistence of excitant effects. Also, convulsions, which may be considered an example of "excitant" actions of opiates in dogs, do not become manifest during withdrawal of morphine in these animals. Furthermore, well defined abstinence signs follow abrupt withdrawal of barbiturates after a period of addiction (Isbell and coworkers, 182) and yet such drugs do not possess notable excitant properties Caffeine withdrawal headache appears to be a definitely established phenomenon (Dreisbach, 90; Dreisbach and Pfeiffer, 91), but it is obvious that occurrence of headaches during abstinence from caffeine is not due to the persistence of the usual action of caffeine itself.

D. Basal metabolic changes

Barbour, Porter and Seelye (22) reported that in dogs a single injection of morphine lowers basal metabolism for about eight hours, and that this is followed by an increase in metabolism during the next 20 hours. The basal metabolism of dogs increased during addiction to a daily dose of 10 mg./kg. of morphine and diminished gradually during withdrawal. In man, however, Williams and Oberst (367) found that the basal metabolic rate was reduced slightly by small doses and definitely after large doses. Basal metabolic rate continued to fall slightly during addiction and rose above normal during the early abstinence period.

E. Water metabolism

On the basis of results of treatment of the morphine abstinence syndrome in man with euphyllin, Adler (2, 3) concluded that hydration occurs during addiction and is related to the genesis of withdrawal signs. Barbour, Hunter and Richey (21) reported that withdrawal of morphine in dogs produces hydration of the blood and probably of the tissues in general. Williams (366) found in man that morphine addiction with strong physical dependence is associated with blood hydration; during withdrawal there is a temporary decrease in hydration but a true concentration does not occur. Detrick and Thienes (88) found that in rats the tissues exhibited a moderate degree of edema after six weeks of morphine addiction; this was greatest for the skin, and least for the brain. On the first day of withdrawal there was a partial or complete recovery from the edema, but a tendency to relapse occurred on the second or third day. Rats kept on a high calcium diet and given injections of parathyroid extract exhibited a greater loss of tissue water during withdrawal and a lesser tendency to relapse, and also showed few withdrawal signs, whereas rats on a calcium-poor regimen showed definite abstinence phenomena.

In contrast with these observations on the role of hydration in the genesis of the morphine abstinence syndrome, Isbell (176) found that in man plasma volume was not altered during addiction to morphine, although the proportion of plasma to cells was increased due to a mild secondary anemia. Increase in extracellular fluid volume occurred after large doses or during progressive increase of dose, but returned to normal when a stable dose level was maintained. Isbell concluded that

it is unlikely that excessive body hydration plays a significant role in the production of physical dependence to morphine in man. Also, during experimental hydration of subjects in the course of investigations of the effects of pitressin hydration on the electroencephalogram, Wikler (349) observed no signs resembling those of morphine abstinence, nor were such phenomena exhibited by the patients during the period of diuresis following cessation of pitressin hydration.

F. Reappearance of acute effects of morphine during abstinence

On the basis of their work on "acute" tolerance to morphine in dogs, Schmidt and Livingston (291) suggested that when the concentration of morphine in certain cells reaches a critical level tolerance develops, and when this falls the depressive effects of morphine may again be manifested. In analogy with this hypothethetical course of events may be mentioned the "yen sleep" which occurs during the early phases of morphine abstinence in man. Similarly, Altschul and Wikler (6) observed that, during the severe abstinence syndrome which develops on abrupt withdrawal of keto-bemidone, slow activity reappears in the electroencephalogram even though considerable degrees of tolerance to the slowing effect of repeated administrations of the drug had been developed prior to withdrawal. These authors, however, offered as an alternative explanation the suggestion that the slow activity in the electroencephalogram during keto-bemidone abstinence was due to cerebral vasoconstriction consequent to the intense autonomic discharges which occur during this period. The hypothesis of Schmidt and Livingston, however, is in accord with observations on the effects of non-opiate drugs, such as those of Kuyer and Wijsenbeek (202). The latter found that when physostigmine, pilocarpine, muscarine, histamine or epinephrine was added to bath fluid in which isolated gut or uterus of the cat, rabbit or guinea pig was immersed, the characteristic effects of these agents subsided after some time; when the fluid was replaced by solutions containing no drugs, the characteristics of each agent were again manifested. They termed this phenomenon "detoxification-excitation" in the case of excitatory agents, and "detoxification-inhibition" in the case of inhibitory drugs.

G. Cholinesterase inhibitory action of morphine

The demonstration by Bernheim and Bernheim (32) that cholinesterase activity is greatly inhibited by small concentrations of morphine *in vitro* has evoked considerable interest in the possible roles that such an action may play in the actions of morphine and other drugs on the nervous system. This finding has been confirmed by Eadie (100) and by Wright and Sabine (378). Slaughter and Lackey (312) were unable to demonstrate the anticholinesterase action of morphine on dog blood *in vitro*, but found that subcutaneous injection of morphine in dogs resulted in a lowering of serum cholinesterase activity. Slaughter (309) has reported that injections of neostigmine reduces tolerance and physical dependence to morphine in dogs. Slaughter and Treadway (313) have also reported that neostigmine decreases the urinary output of morphine in both habituated and non-habituated dogs, and suggested that the potentiation of analgetic and hyp-

notic effects of morphine by neostigmine, which they observed was due to the retention of morphine in the body. However, Wikler and Frank (361) found that, in chronic spinal dogs, physostigmine produces changes in the hindlimb reflexes which resemble those seen during abstinence from morphine or methadone, and have suggested that cumulative depression of cholinesterase activity in the nervous system may contribute to the genesis of the withdrawal syndrome. This hypothesis has not yet been investigated experimentally.

Schuetz (292) observed that, when phenobarbital was withdrawn abruptly, epileptics who had been treated with this drug for long periods of time showed an increased number of convulsions while the serum cholinesterase level was still low, and that the incidence of convulsions decreased to the pre-medication frequency when serum cholinesterase returned to normal levels. On this basis, he postulated a theory of drug addiction based on two effects of the drug: (1) "D", a direct effect, measured in the case of barbiturates by the number of fits, and (2) "C", a counter-adaptation, reduction in serum cholinesterase. He stated that ". . . the condition for an increased demand for a drug after it is withheld (addiction), or that higher doses are gradually needed to obtain the same effect (tolerance), might generally be expressed thus dD/dt is greater than dC/dt, where t is time, and both dD/dt and dC/dt are positive in drug addiction, immediately after the drug is withheld, and negative in drug tolerance, immediately after the drug is given." However, Isbell and coworkers (182) were unable to demonstrate any significant changes in serum cholinesterase during experimental addiction to barbiturates in non-epileptic post-addicts.

CONCLUSIONS

In recent years, there has been a general trend toward seeking explanations of the actions of drugs on the nervous system not on the basis of gross anatomical localizations, but on neuron systems and mechanisms which extend throughout the neuraxis. This trend appears to be in the right direction, for earlier interpretations based on stimulation or depression of "the spinal cord" or "the cerebral cortex", etc., have proven inadequate, since drugs like morphine exert both types of effect at each level of integration in the nervous system. Nevertheless, caution must be exercised in transferring conclusions drawn from data obtained from studies on one part of the nervous system to other parts. Thus, because of similar actions of certain doses of morphine, barbiturates and mephenesin in the spinal animal, a depressant effect on internuncial neurons has been invoked to explain the general action of each drug. Because of their different clinical actions, this cannot be the sole explanation. Furthermore, certain functions in the central nervous system which are presumably mediated by internuncial activity are affected differently by these agents. Thus barbiturates alter spontaneous electrical activity throughout the nervous system, whereas mephenesin affects such activity very little. On the other hand, mephenesin depresses facilitatory and inhibitory mechanisms markedly throughout the neuraxis, whereas morphine does so only to a mild degree. On the basis of evidence to date, however, it appears that all three drugs do possess in common the ability to depress after-discharge consequent to afferent nociceptive

stimulation, which may play an important role in the subjective experience of pain. The differences between the effects of these drugs on other types of "internuncial" activity, however, may explain why they are not all analgesics in the clinical sense of the term. Thus, in doses sufficient to depress after-discharge to comparable degrees, barbiturates also depress reticular activating systems in the midbrain and diencephalon and produce marked impairment of consciousness; mephenesin depresses postural integrating centers in the brain stem and spinal cord, and produces muscular weakness and paralysis. Morphine possesses these properties only to a mild degree, and indeed, actually enhances reflex responses to non-nociceptive stimuli such as muscle stretch, sudden auditory and tactile stimuli, etc. This may explain why morphine affords relief of pain without producing anesthesia or paralysis, although a tendency to fall asleep, if undisturbed, and slight muscular weakness may be present. With further study of the effects of these drugs on facilitation and inhibition, and the electrical events which result in neuronal depolarization and recovery in the nervous system, the reasons for the specificity of morphine action may become clearer.

New tools for further studies on the mechanisms of tolerance have been developed with the discovery of free and bound forms of morphine in the urine. All parts of the nervous system are involved in the genesis of the morphine abstinence syndrome. In the dog, the essential features of this phenomenon may be observed in the absence of the cerebral cortex. In man, the frontal lobes play a dominant role in the genesis of suffering, craving and purposive behavior during abstinence from morphine; they may also contribute to the genesis of the non-purposive signs which appear after withdrawal of the drug. The pattern of the abstinence syndrome appears to be in the nature of an adaptive response. Whether such homeostatic mechanisms are developed in response to effects of morphine on the nervous system or on other organs needs to be clarified by further experimentation.

From the data analyzed in this review another conclusion may be drawn which relates to the philosphy of research, particularly in fields where widely differing technics are employed (Wikler, 353). In the case of clinical problems relating to the use of analgesics, the most important phenomena to be investigated are expressed in the frame of reference of subjective experience,—relief of pain, euphoria, addiction, etc. Essentially, "explanations" of such phenomena are descriptions of the changes produced in the organism by administration of analgesics, in terms other than those of subjective experience. In addition to purely introspective technics, one must employ methods which yield data that are expressed in such different frames of reference as performance in psychologic tests, physiologic responses to stimuli, changes in the spontaneous electrical activity of the nervous system, biochemical and anatomic changes, etc. In each frame of reference, the data acquired are related to a great many variables, the number and configuration of which differs from those related to data acquired with other technics, although some overlapping may exist. In general, the more widely the technics differ, the less, relatively, will be the extent of overlap. It is therefore not enough to look for psycho-physiological or psycho-biochemical "correlations". One must also search for the "common denominators" or the variables that are common to the data ac-

quired with all technics utilized. It should also be realized that such variables may not be indispensable components of the clinical phenomenon under investigation, but recognition of them may lead to therapeutic applications in the clinic or open new fields for further research.

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