SITES OF ACTION OF SOME CENTRAL NERVOUS SYSTEM DEPRESSANTS[1]

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Even in a relatively restricted area of interest such as the action of drugs affecting the central nervous system, a reviewer is faced with an enormous accumulation of literature which defies tabulation let alone assimilation of its contents. Fortunately there is a new abstracting service made available by the Psychopharmacology Service Center of the National Institute of Mental Health in the form of monthly psychopharmacology abstracts. This at least calls one's attention to current pertinent publications. Several yearly reviews (7, 8, 131) tend to further consolidate the literature into reasonable reports of progress. Few investigators have tried to synthesize the divergent views on data obtained from many animal species as to how and where drugs act in the central nervous system. The proposed sites of drug action of Himwich (80, 81) & Gangloff, Monnier and associates (58, 59 60, 120 to 124) illustrate perhaps the boldest attempts in defining the sites of action of various centrally acting agents.

Although interest in drugs affecting the central nervous system stems primarily from their application to human therapeutics, of necessity animals must be used for most neuro- and psychopharmacological studies. All biological scientists are plagued with the problem of inter- and intraspecies variability. Species variation with regard to drugs affecting the central nervous system is especially marked. The anatomical variations of brain complexity increase immensely the possibility of variability. Among the many human sources of error is the tendency of most investigators to use their own pet techniques involving one or the other animal species. Seldom, if ever, does one read of investigators using three, four or more animal species in order to determine if the effects observed apply to one or a majority of available experimental animals. Much too often, an investigator attempts to transfer his data from one animal species to man not bothering to determine if the effects observed are species specific. In studying the actions of a drug on a given neuronal system it is a common human fault to use drugs in ridiculously large dosages if necessary to produce an effect. The author is as guilty as anyone of this error. The problem will always be with us as to whether the effects reported involve physiologic, pharmacologic, or toxicologic amounts. The Killams (94) have summarized well this and other methodological problems. The fact that neuropharmacologists use drastic surgical procedures that cause profound brain injury, chronic implantation techniques which produce

[1] The survey of the literature pertaining to this review was concluded in August 1961.

glial scars at electrode tips and obtain results with electrical methods which defy quantification further complicates the picture. Add to this the complexity of the central nervous system and a startling picture of chaos regarding the neural mechanisms of drug action emerges. Too often it is assumed that a drug acts where a recording or stimulating electrode was placed. For example, an electrode is placed in the ascending reticular activating system in order to elicit EEG arousal which is recorded from the cerebral cortex. A drug which blocks EEG arousal or shortens it may act: (*a*) In the reticular formation in the general area of stimulation. (*b*) On areas of the diffuse thalamic projection system or extrathalamic structures projecting to cerebral cortex. (*c*) On neurons of the various layers of cerebral cortex. (*d*) On the cerebral neuronal system projecting fibers back into the reticular formation. (*e*) On neurons distant to the circuits described above but projecting into or modulating their activity. (*f*) Through non-neuronal vascular or metabolic mechanisms (such as regulation of passage of various substances across the blood-brain barrier) which will influence all of the neuronal circuits described above. Yet it is commonly assumed that a drug blocking or reducing EEG arousal has actions on the reticular formation per se.

It is not too surprising that anyone should suggest that as of August, 1961, we are still quite ignorant of the precise neural mechanisms of the action of any drug affecting the central nervous system. The pessimist (or realist) perhaps may say this of any drug affecting any organism. It has been said that "One can teach a pretty good course in CNS pharmacology on the assumption the calvarium is filled with cotton." While this may be true of some pharmacological curricula, it is hoped that this cursory review will show that this is a foolish attitude inasmuch as evidence is available to suggest that several drugs affecting the central nervous system have selective effects on various portions of it. The past decade has seen a remarkable increase in basic research on the neural mechanisms of drug action obviously spurred on by the clinical usefulness of "tranquilizers" and "psychic energizers," terms which to date defy precise pharmacological definition.

It is the purpose of this review to cover a very limited group of central nervous system depressants in order to formulate working hypotheses of their neural mechanisms of action based upon available electrophysiological evidence which has come to the author's attention. Apologies are offered to colleagues whose research publications have escaped the author's cursory literature survey. The extensive analyses and hypotheses of Grundfest & Purpura will not be discussed. In the past few years these investigators have reviewed their own and related data (64, 65, 133, 134). Similarly, the neurohumoral aspects of central nervous system function will not be reviewed inasmuch as several excellent summaries of this subject have appeared (29, 52, 127). Specific reviews on acetylcholine (70, 71), catechol amines (142, 167), serotonin (26, 61, 126) and γ-aminobutyric acid (46, 141) are available. The very broad area of central nervous system stimulants will also not be reviewed. Several important original papers are available written by investiga-

tors summarizing their own and related contributions. These include Bradley and his associates (18 to 22) and Monnier & Krupp (124). Richards (138) has reviewed the pharmacological basis and clinical use of analeptics in barbiturate poisoning. Several symposia on antidepressants including the amine oxidase inhibitors (151 to 154) and imipramine (25) are available. The actions of hallucinogens have also been reviewed (48). A number of symposia on neuro- and psychopharmacology or on specific drugs have also appeared for both scientific and advertising purposes (49, 157, 158).

Barbiturates

Fast waves are observed in the human EEG following administration of low doses of various barbiturates. These were reported many years ago by numerous clinical electroencephalographers [see Brazier (23)]. In animals, similar fast wave EEG activity may be observed. It is often seen in animals with chronically implanted electrodes including the dog (43) and monkey (42). The neural origin of barbiturate fast waves is unknown. Brazier (23) has offered evidence based upon bipolar recordings from a series of implanted electrodes reaching from the convexity of the surface of the frontal cortex to the orbital surface of the frontal lobes in man that such fast wave activity is recorded better from cerebral cortex than underlying white matter. Furthermore, a reversal in potential of the fast wave activity was seen in the deeper layers of the cortex indicating a superficial site of origin. However, mental patients subjected to various lobotomies have a marked diminution of the amplitude of continuous fast wave activity induced with light thiopental anesthesia after undercutting or complete isolation of a small portion of frontal cortex (45, 78). The fast wave activity involved in the "suppression bursts" recorded in isolated cerebral cortex is unrelated to the anesthetic used. Most animal evidence suggests that the barbiturates depress the cerebral cortex.

Years ago Keller & Fulton (88) showed that pentobarbital and phenobarbital increase the threshold for electrical stimulation of the motor cortex of monkeys. Phenobarbital was much more specific in this regard in that it caused a marked elevation of threshold in non-anesthetic doses as compared to pentobarbital. More recently, Delgado & Mihailović (34) have confirmed these findings for phenobarbital (15 mg/kg, ip) given to monkeys with chronically implanted electrodes. In addition to elevating the threshold for a minimal motor response in area 4, it elevated the threshold in area 6 as well as in nucleus anterior dorsalis of the thalamus, and in the hippocampus. Phenobarbital raised the threshold for local motor convulsions and shortened seizure duration. The recovery time for convulsive capacity of areas 4 and 6 was also prolonged by this agent. These investigators also showed that phenobarbital elevated the threshold for electrical afterdischarge. The threshold for motor cortical electrical afterdischarge was increased 260 per cent, that for amygdala 160 per cent and that of nucleus anterior dorsalis of the thalamus 351 per cent. Evidence for the differential threshold elevating proper-

ties of phenobarbital has also been provided by Gangloff & Monnier (58) using the unanesthetized rabbit. Contrary to the reports of others these investigators showed that phenobarbital (30 to 60 mg/kg, by mouth) reduced the threshold for induced electrical afterdischarge in the sensorimotor cortex.

On the other hand, the threshold for electrical afterdischarge from stimulating the lateral thalamus was markedly elevated and the duration of afterdischarge reduced. The threshold for afterdischarge elicited in the dorsal and ventral hippocampus was also elevated, but not as much. The duration of afterdischarge was not markedly altered. The finding that phenobarbital lowered the threshold of the sensorimotor cortex is difficult to understand. Yet, it has been shown by Schütz & Caspers (146) that low doses of phenobarbital (20 to 40 mg/kg, im) in rats may facilitate and provoke epileptic type electrical discharges in the cortex, particularly when the cortex is injured. Such an effect may, of course, be secondary to a "release phenomenon" of the cortex due to depression of an ascending inhibitory system of the type proposed by Brazier (23), Purpura (133) and others (39). Additional scientific evidence supporting the clinical usefulness of phenobarbital as an anticonvulsant agent as compared to pentobarbital has been provided by Aston & Domino (5). Phenobarbital was shown to elevate motor cortical thresholds in monkeys with chronically implanted electrodes in doses which only minimally increased reticular thresholds. Pentobarbital, however, depressed both motor and reticular thresholds to a similar extent. In contrast diphenylhydantoin elevated the cortical motor threshold in doses having no significant effect on reticular thresholds. These findings are in agreement with those of Martin *et al.* (113) who found that diphenylhydantoin in doses up to 30 mg/kg had no effect on EEG arousal elicited from stimulation of the reticular formation or on the spindles of the *cerveau isolé* cat preparation. Phenobarbital in equal doses and more (30 to 70 mg/kg, iv) depressed EEG arousal. Doses of phenobarbital one third as large as those used in intact animals depressed the frequency of spindles and induced more slow waves in the *cerveau isolé* preparation. Takaori & Deneau (163) also have observed that pentobarbital (10 and 20 mg/kg, im) elevates the motor cortical threshold in monkeys with chronically implanted electrodes.

The predominant EEG effect of barbiturates in acute animal preparations is the appearance of spindles and generalized slow wave activity in intact cerebral cortex. These have been reported by numerous investigators. Pentobarbital and amobarbital also cause marked EEG slowing in the caudate nucleus of cats (74). Pentobarbital and related barbiturates also produce slow waves in the isolated cerebral cortex preparation of both cat (41) and dog (137). The threshold of induced afterdischarge in the isolated cortex of dogs is elevated and its duration shortened by thiopental and phenobarbital (42). Phenobarbital elevates the threshold for induced afterdischarge in nucleus anterior dorsalis thalamus of monkeys (34) and the lateral thalamus of rabbits (58). The depressant effects of barbiturates on the recovery cycles of

specific relay nuclei of thalamus were described many years ago by Marshall and recently have been confirmed and extended by King *et al.* (100). The latter investigators have shown that low doses (5 to 10 mg/kg, iv) of thiopental and pentobarbital prolonged the latencies, increased the amplitude and broadened the shape of single evoked responses through nucleus ventralis posterior. Recovery cycles were only slightly prolonged with facilitation of the amplitude of the second responses. In general, these effects were similar to those associated with EEG synchrony and were attributed to a depression of the ascending influences of the reticular formation. In anesthetic doses (30 mg/kg) the barbiturates markedly increased the latency, reduced the amplitude and prolonged the recovery time of thalamic responses suggesting a direct depressant effect on transmission through this specific thalamic relay nucleus. The collective data in the literature indicate that anesthetic doses of barbiturates have a depressant action directly upon the thalamic relay nucleus for each afferent modality (100). Takaori & Deneau (163) have shown that pentobarbital (10 and 20 mg/kg, im) increased the threshold for alerting and masticatory movements from stimulation of nucleus ventralis posterior lateralis in monkeys.

It is well established (39, 86, 99) that barbiturates in low doses (5 mg/kg, iv) enhance recruiting responses following low-frequency stimulation of nuclei of the diffuse thalamic projection system of cats. In anesthetic doses (30 mg/kg, iv) recruiting responses are somewhat diminished in amplitude and there is a lack of one to one following (39). Perhaps this is indicative of prolonged neuronal recovery cycles in this system as well. In cats with chronically implanted electrodes pentobarbital (10 mg/kg, iv) elevates the threshold for both EEG arousal and gross behavior elicited following high-frequency stimulation of various nuclei of the diffuse thalamic projection system (96). No marked separation of gross behavioral and EEG arousal was noted after pentobarbital as was the case with chlorpromazine. These results indicating a depressant effect of pentobarbital are in marked contrast to the facilitating effects on recruitment elicited by low-frequency stimulation of the same nuclei. The latter appears to be a "release phenomenon" due to depression of the brainstem reticular formation (39).

For many years barbiturates have been known to depress hypothalamic structures (see 173). Evoked potentials in the hypothalamus of the cat are depressed by barbiturates such as pentobarbital. Feldman *et al.* (51) found that the hypothalamus was even more sensitive to barbiturates than the midbrain reticular formation. Large anesthetic doses of pentobarbital caused the appearance of high voltage, long latency (60 to 160 msec) responses in the hypothalamus, intralaminar nuclei of the thalamus and midbrain reticular formation following sciatic nerve stimulation in the cat. These were suggested to be the "secondary response" of *Forbes* recorded at brainstem levels (50). Recently, Takaori & Deneau (163) have shown that pentobarbital (10 mg/kg, im) slightly elevated the threshold for arousal and startle arising from stimu-

lation of the posterior hypothalamus of monkeys. A marked elevation in electrical threshold occurred with 20 mg/kg of pentobarbital.

The limbic system appears to be prone to the depressant effects of various barbiturates. Pentobarbital in low doses (5 to 10 mg/kg, iv) has been shown to cause a marked elevation in threshold and decrease in duration of afterdischarge from electrical stimulation of the amygdala or hippocampus in cats (96). Somewhat similar findings were reported by Takagi & Ban (159) using hexobarbital (10 to 20 mg/kg, iv) in high spinal cat preparations. Repetitive electrical stimulation of the precommissural fornix results in hippocampal electrical seizures. Following hexobarbital these were markedly reduced in duration with an elevation in threshold. Single shock stimulation of the fornix elicits a potential in the hippocampus which is not affected by 10 mg/kg of hexobarbital in high spinal cats. Post-tetanic potentiation of this response is blocked by these doses of hexobarbital (159). Similar effects of hexobarbital were demonstrated on post-tetanic potentiation elicited by stimulation of the amygdala on potentials recorded in the hippocampus and post-tetanic potentiation elicited by stimulation of the hippocampus on potentials recorded in the lateral hypothalamus. In the monkey Takaori & Deneau (163) have demonstrated that pentobarbital (10 and 20 mg/kg, im) increased the threshold for all three behavioral components described by Kaada following electrical stimulation of the amygdala. They have also shown that 20 mg/kg of pentobarbital increases the threshold and shortens the duration of electrical afterdischarge from stimulation of the hippocampus. Aston & Domino (5) have reported that both pentobarbital and phenobarbital elevate the threshold for electrical afterdischarge in the hippocampus of monkeys.

Since the studies of French *et al.* (54), it has been well established that small amounts of barbiturates and other anesthetics decrease evoked reticular potentials (4, 50, 108). French (53) has reviewed the actions of drugs on this system. EEG arousal, elicited by stimulation of the brainstem reticular formation in cats and monkeys, is depressed by small doses of barbiturates (4, 39, 54, 99). King *et al.* (100) have shown that the relative recovery period of responses to peripheral nerve stimulation recorded from the midbrain reticular formation of cats is depressed by small doses of pentobarbital (5 mg/kg, iv). In cats with chronic brain electrodes pentobarbital (10 mg/kg) raised the threshold for behavioral arousal more than the threshold for EEG desynchronization (96). Pentobarbital (10 to 20 mg/kg, im) increases the threshold for EEG and behavioral arousal in monkeys with chronic implanted electrodes (163).

Considerable data are available on the spinal cord depressant effects of barbiturates. Small doses of pentobarbital and diallylbarbituric acid depress polysynaptic pathways more than monosynaptic pathways [see review (40)]. Phenobarbital (2.5 to 10 mg/kg, iv) depresses the flexor reflex of high spinal cats (130). Large doses of pentobarbital depress both mono- and polysynaptic reflexes and stabilize the membrane potential of spinal motoneurons (44).

MEPROBAMATE

In man, oral doses of 1600 and 2000 mg of meprobamate produce barbiturate-like fast waves of 20 to 30 cps in the cortical EEG, especially in the parietal areas (130). Such EEG fast-wave activity also has been observed by many others (15, 76, 77, 118, 165). Bokonjic & Trojaborg (15) have studied the effect of a wide range of doses of meprobamate (15 to 400 mg/kg, orally) on the EEG of patients during treatment, intoxication, and after abrupt withdrawal. In certain respects, meprobamate and the barbiturates have similar effects on the EEG. Both drugs induce fast wave activity which is more pronounced during drowsiness and disappears during sleep. Both drugs show evidence of tolerance to these EEG changes. After abrupt withdrawal of both agents paroxysmal EEG changes are noted during photic stimulation. In confirmation of Pfeiffer *et al.* (130) the cortical distribution of the fast frequency activity seems to differ. After meprobamate the EEG fast-wave activity tends to be most pronounced in the parietal areas, while after barbiturates it is most pronounced frontally, fronto-temporally or parietally. After withdrawal of meprobamate the paroxysmal EEG changes rarely persist as long as two weeks. After withdrawal of barbiturates the changes may last two months. The principal EEG differences between meprobamate and barbiturates occur after ingestion of toxic doses. After meprobamate poisoning the fast waves persist even during the period of unconsciousness. Frequencies of less than 6 cps rarely are seen. The EEG usually is normal 48 hr after doses as large as 400 mg/kg orally. The EEG fast-wave activity persists only with small doses of barbiturates. After large toxic doses the fast-wave activity is replaced by 2 to 6 cps activity of high amplitude. It may take weeks for the EEG to become normal although admittedly this could be secondary to brain damage due to hypoxia as a result of severe respiratory depression.

In intact cats immobilized with gallamine, meprobamate in doses of 10 to 30 mg/kg, iv, does not consistently alter the spontaneous EEG of the cortex and subcortex (57). In doses of 40 mg/kg, iv, the drug causes a slight increase in the fast components of the EEG. Sufficient research with meprobamate in isolated cortex preparations has not been available to warrant any definite conclusion on the cortical actions of this compound. In view of its similarities to certain barbiturates it probably has cortical depressant effects but to a lesser degree.

In intact curarized cats, meprobamate, in doses of 20 mg/kg, iv, produces synchronization of the spontaneous EEG selectively in various specific and diffusely projecting thalamic nuclei including the lateral geniculate, n. ventralis lateralis, n. ventralis posteromedialis, and n. centrum medianum (74). These investigators concluded that EEG slowing in the thalamic nuclei occurred as one of the earliest manifestations of the electrical effects of meprobamate. Similar slow-wave activity following meprobamate in the caudate nucleus, pallidum, and amygdala has been seen in cats and humans (6). EEG slow waves were also seen by Berger *et al.* in nucleus lateralis pos-

terior of the thalamus of monkeys following 20 mg/kg, iv, of meprobamate (13). These changes were claimed to be characteristic for meprobamate and different from those of other central nervous system depressants. Frequent waxing and waning and occasional spindling occurred. After large doses of meprobamate (120 mg/kg) generalized slow waves of increased amplitude were observed. Even after these large doses the thalamus showed changes to a greater degree. In contrast 5 mg/kg of pentobarbital produced generalized slowing and spindling more apparent in the cerebral cortex and caudate nucleus than in the thalamus or hypothalamus. Amobarbital in similar dosage in two cats was reported to cause more high voltage activity in the thalamus than pentobarbital. Mephenesin in doses of 40 mg/kg had no effect. Chlorpromazine (10 mg/kg, iv) and reserpine (2.5 mg/kg, iv) yielded inconsistent effects although thalamic slowing sometimes was also seen. In intact cats immobilized with gallamine, Gangloff (57) observed that in doses as low as 10 mg/kg, iv, meprobamate elevated the threshold for EEG recruiting following stimulation of nucleus centralis lateralis of the thalamus. However, after lesions of the midbrain reticular formation, meprobamate even in doses of 50 mg/kg had no effect on the threshold for recruitment. Takaori & Ohata (164) have observed that in doses of 20 to 50 mg/kg, iv, meprobamate produced no change in recruiting responses recorded from the cerebral cortex to low-frequency stimulation of nucleus centrum medianum in high spinal cats. Large doses of 80 mg/kg increased EEG slow waves and background activity obscuring the effect if any on recruitment.

Bovet *et al.* (16) studied the effects of a large range of doses of meprobamate (10 to 100 mg/kg, iv) in comparison to other CNS depressants on the EEG arousal and alarm reaction of rabbits in which the hypothalamus was stimulated. They showed that meprobamate inhibited the alarm reaction and partially depressed arousal from hypothalamic stimulation.

Meprobamate causes a decrease in electrical afterdischarge in both the amygdala and hippocampus of acute cat preparations (Kletzkin & Berger, 101). These effects occurred in relatively low doses (20 mg/kg, iv) suggesting a more selective effect on limbic structures than barbiturates. However, Takagi & Ban (159) were unable to show that 20 mg/kg of meprobamate given intraperitoneally had any suppressive effect on hippocampal afterdischarge produced by repetitive stimulation of the precommissural fornix of high spinal cats. The duration of seizures was slightly shortened after 40 mg/kg of meprobamate without any change in threshold. Schallek & Kuehn (143) reported a shortening of septal afterdischarge caused by electrical stimulation of the septum following 20 mg/kg, iv, of meprobamate in intact cats immobilized with decamethonium.

Doses of 20 mg/kg, iv, of meprobamate which depress limbic system afterdischarge have negligible effects on the threshold and duration of EEG arousal from stimulation of the reticular formation of the brainstem. Kletzkin & Berger (101) pointed out that 20 mg/kg of meprobamate had no effect on cerebral cortical and hippocampal arousal elicited by stimulation of the

reticular formation in postether anesthetized intact cats as opposed to the effects of various barbiturates which depressed both limbic system afterdischarge and EEG arousal. In intact cats immobilized with gallamine, Gangloff (57) observed that meprobamate in doses up to 80 mg/kg, iv, did not usually alter the threshold of EEG arousal from stimulation of nucleus centralis lateralis of the thalamus, midbrain reticular formation, and sciatic nerve. Only in doses reported to produce gross behavioral sleep (100 to 200 mg/kg) was there a slight increase in the threshold for EEG arousal. In animals with midbrain reticular lesions low doses (10 or 20 mg/kg, iv) consistently increased the threshold for EEG arousal following stimulation of sciatic nerve, rostral reticular formation and nucleus centralis lateralis of the thalamus. Takaori & Ohata (164) have observed that 20 mg/kg, iv, of meprobamate had no effect on EEG arousal following stimulation of the midbrain reticular formation in high spinal cats. Larger doses (50 to 80 mg/kg) shortened the duration of EEG arousal. Kletzkin & Swan (102) compared the effects of meprobamate to those of pentobarbital in cats under succinylcholine on evoked cortical, medial geniculate, nucleus centrum medianum and midbrain reticular formation potentials due to click stimuli. Doses of 40 mg/kg, iv of meprobamate had no effect on the specific ascending system as recorded from the medial geniculate and temporal cortex. The amplitude of the responses from the nonspecific afferent system as recorded from the reticular formation, nucleus centrum medianum, and amygdala were slightly enhanced by meprobamate. Doses of 80 mg/kg of meprobamate caused little change except for an enhancement of one-third of the evoked responses in the reticular formation. Anesthetic doses (30 to 40 mg/kg) of pentobarbital abolished or depressed the responses in nucleus centrum medianum, nucleus dorsalis medialis, and the reticular formation. Evoked responses in the specific relay system were depressed in amplitude. The published records also indicate a widespread distribution of the "secondary response of Forbes" following the administration of pentobarbital. It is unfortunate that the authors did not study the effects of larger doses of meprobamate. Their statistical comparison of 40 mg/kg of meprobamate to 30 mg/kg of pentobarbital is completely misleading because they were not using comparable doses of the two drugs.

The actions of meprobamate upon spinal cord reflexes were originally described by Berger (12). In chloralose or diallylbarbiturate anesthetized cats 40 mg/kg of meprobamate given intravenously depressed both the patellar and flexor reflexes. Polysynaptic reflexes such as the flexor, crossed extensor and linguomandibular reflexes were more depressed than monosynaptic reflexes such as the patellar. The onset of action of meprobamate was much slower than after mephenesin. Subsequently, Hendley *et al.* (73) claimed that in similar preparations meprobamate, in doses of 50 to 80 mg/kg, iv, usually had no effect on the amplitude of the patellar reflex while it abolished the flexor reflex. Interestingly, the linguomandibular reflex was abolished only after large doses of meprobamate.

Abdulian *et al.* (1) studied the effects of meprobamate in comparison to mephenesin, pentobarbital, and SKF 1045 on inhibition and facilitation of the patellar reflex evoked by stimulation of the ipsilateral or contralateral sciatic nerve in high spinal cats. As a guide for dose levels to be used in the cat experiments, relative potency for producing ataxia, loss of the righting reflex and death were determined in mice. The effects of mephenesin and SKF 1045 differed from those of meprobamate and pentobarbital. In doses producing ataxia in mice, mephenesin and SKF 1045 caused only a slight decrease in the amplitude of the patellar reflex in cats. On the other hand in subataxic doses in mice, meprobamate and pentobarbital produced a depression comparable to that of mephenesin and SKF 1045 of the patellar reflex. It was also shown that inhibition of the patellar reflex was depressed by all drugs studied. The depression of inhibition occurred with subataxic doses that did not markedly depress the patellar reflex, but did depress its facilitation. The complexities of stimulating the entire sciatic nerve make these latter data difficult to interpret. Pfeiffer *et al.* (130) showed in spinal cats that meprobamate (40 mg/kg, iv) abolished the flexor and depressed the patellar reflex. Comparable effects were produced by 2.5 mg/kg of phenobartital or 20 mg/kg of mephenesin. DeSalva & Ercoli (37) compared the effects of meprobamate with styramate, phenaglycodal, and chlorpromazine on the augmentation of the patellar reflex by contralateral sciatic nerve stimulation (polysynaptic) and the patellar reflex itself (monosynaptic) in decerebrate and spinal cats. An average dose of meprobamate (27.5 to 35 mg/kg, iv) blocked the effects of sciatic nerve stimulation to a similar extent in decerebrate and spinal animals without affecting the patellar reflex. In contrast, styramate, phenaglycodal, and chlorpromazine were more effective in depressing the effects of sciatic nerve stimulation in decerebrate than spinal animals. DeSalva & Oester (38) extended these findings by comparing meprobamate and many other central nervous system depressants on the effects of contralateral and ipsilateral stimulation of the sciatic nerve on the patellar reflex in high spinal cats. They concluded that, in general, polysynaptic reflexes are more depressed than monosynaptic reflexes but that in appropriate doses monosynaptic reflexes are depressed as well by a variety of centrally acting drugs. Wilson (174) has shown that the monosynaptic flexor and extensor reflexes of the decapitate cat in which selected peripheral muscle nerves are stimulated and the potentials recorded in the ventral root are depressed after cumulative doses of 100 mg/kg, iv, of meprobamate. Initial doses of 30 to 40 mg/kg have unpredictable actions. Inhibitory pathways, both direct and disynaptic, were highly resistant to meprobamate. The drug did not affect the input-output relations of monosynaptic reflexes. Wilson suggests this agent acts as a general depressant of excitatory synaptic transmission. Wilson & Talbot (175) studied the effects of meprobamate, administered intravenously in cumulative doses of 40 mg/kg every 40 min to decapitate cats, on recurrent facilitation or inhibition of monosynaptic potentials elicited by stimulating dorsal roots and recording in cut peripheral nerves. Recurrent facilitation or

inhibition was initiated by antidromic impulses entering the cord via the intact ventral roots. Total doses of 210 to 400 mg/kg were necessary to abolish recurrent facilitation. Such large doses did not decrease recurrent inhibition and in fact prolonged the duration of the inhibition. Pentobarbital in doses of 5 to 10 mg/kg, iv, had the same action as meprobamate on recurrent conditioning. However, these effects were accompanied by a more marked depression of the monosynaptic reflex in contrast to the doses of meprobamate that had the same action on conditioning.

Methaminodiazepoxide

A broad spectrum of psychopharmacological activity has been claimed for this agent [Randall *et al.* (136)]. There is no question that it is a member of a new chemical class of compounds with central nervous system depressant effects. It has been claimed that the taming effects of methaminodiazepoxide in monkeys occur in doses far below the ataxic dose contrary to the taming effect observed with chlorpromazine, meprobamate, and phenobarbital (135). Methaminodiazepoxide has many properties in common with meprobamate and phenobarbital, particularly in animals, with regard to its anticonvulsant effects and slight skeletal muscle relaxant actions. It has been claimed that the drug has less of a hypnotic effect than these other agents. Strangely, it seems to be more effective by the oral than the subcutaneous route.

Very few neuropharmacological studies have been published on this relatively new drug. Schallek & Kuehn (143) have shown that this agent in doses of 10 mg/kg, iv, in intact cats immobilized with decamethonium depresses the duration of electrical afterdischarge from stimulation of the septum, amygdala, and hippocampus. The compound is more potent than meprobamate in depressing the irritability of rats with septal lesions. In doses of 20 mg/kg methaminodiazepoxide blocks EEG arousal from stimulation of the brainstem reticular formation (135). Depression of the flexor reflex in chloralose anesthetized cats was observed in doses of 3 mg/kg, iv. After methaminodiazepoxide, depression of EEG arousal occurred in doses considerably above those which produced depression of the flexor reflex. With meprobamate the dose required for depression of the flexor reflex was 50 mg/kg intravenously while that producing depression of EEG arousal was 40 mg/kg. The dose of pentobarbital required to block EEG arousal was stated to be 1 mg/kg and that causing depression of the flexor, 15 mg/kg. The latter dose seems excessively high compared to other data in the literature.

Morphine

The detailed reviews of Wikler (172, 173) are classics in summarizing available knowledge on the sites of action of morphine and other centrally acting drugs. It has been assumed that the analgesic properties of morphine are caused by an action directly on the central nervous system. Only recently, has evidence been offered that morphine has no significant effect on peripheral nerve endings. In a detailed study on tooth pulp afferents of the

dog, Wagers & Smith (168) have shown that morphine in doses of 2.5 to 5 mg/kg, iv, had no consistent effect on dental nerves and receptors. In contrast, local anesthetics such as lidocaine and procaine (2 to 20 mg/kg, iv) significantly decreased the excitability of pulpal nerves both to electrical and thermal stimulation of the tooth and mechanosensitive neurons of periodontal tissues. It was concluded that local anesthetics but not morphine elevated the threshold for excitation without affecting the ability of the nerves to generate or propagate impulses. Krivoy (104) showed in some interesting *in vitro* experiments that various analgesics including morphine augmented the positive afterpotential and decreased the fidelity with which high frequency evoked potentials could be conducted. Neither procaine nor pentobarbital had these effects, although strychnine also augmented, but in a different way, the positive afterpotential. Levallorphan was able to antagonize the actions of morphine but not those of strychnine. The significance of these *in vitro* data is not certain but it is interesting to note that Krivoy hypothesized that morphine enhanced positive afterpotentials could lead to an exaggerated subnormal period of critical neurons conducting pain impulses within the central nervous system. The hypothesis is certainly worth testing.

The central actions of morphine continue to pose a challenging riddle. Its solution is complicated by very marked interspecies variation. It has been acknowledged generally that morphine has inconsistent effects on the motor cortex. The older literature (see 172) describes no particular change in the motor cortical threshold of rabbits or man. Following large doses of morphine in the dog there is a tendency to respond to local stimulation of the motor cortex with generalized epileptic fits, [Bubnoff & Heidenhain, (24)]. Keller & Fulton (88) reported in one monkey a marked increase in motor cortical threshold after morphine in apparently large doses but insufficient for surgical anesthesia. On the other hand, Deneau & Takaori (36) have failed to find a change in motor cortical threshold in monkeys using more reasonable doses in the order of 3 to 9 mg/kg, sc. Morphine, especially in large doses, apparently depresses other areas of the cerebral cortex. Takaori (162) reported that 6 mg/kg, iv, of morphine in acute high spinal cat preparations depresses the transcallosal response recorded in the contralateral lateral cortex to ipsilateral stimulation. Morphine induced hypotension lasted approximately ten minutes but the depression of the transcallosal response lasted for at least one hour. The older literature on the effects of complete decortication of cats suggests that morphine-induced excitement is still present. On the other hand a prefrontal lobotomy in cats reduces morphine induced excitement but not the hyperthermia (116). The actions of morphine on topical application in a 1 per cent concentration or intracarotid administration in a dose of 125 μg/kg on the isolated cortex of the dog have been described by Crepax & Infantellina (27, 28). A stimulant effect was observed. The threshold of the response to single shocks was lowered, and the afterdischarge in response to repetitive stimulation was enhanced and prolonged. The combined application of physostigmine and morphine produced activity in the isolated cortex

similar to that caused by physostigmine and acetylcholine. The application of atropine did not block the effects of the former combination but it did block the effects of the latter. Crepax & Infantellina suggested the application of 1 per cent morphine to the isolated cortical region as a means of determining if dogs were predisposed to "reflex epilepsy." Using the unanesthetized rabbit, Gangloff & Monnier (59) have described an elevation in threshold of the sensorimotor cortex and a slight prolongation of cortical afterdischarge following large doses (25 to 40 mg/kg, iv) of morphine. Levorphan in large doses (10 mg/kg, iv) elevated the cortical threshold, but did not affect the duration of afterdischarge. Levallorphan in large doses (6 to 15 mg/kg, iv) also elevated the cortical threshold but shortened the duration of afterdischarge. In amobarbital anesthetized cats morphine (6 mg/kg, iv) depressed the second component of the local cortical potential elicited in the suprasylvian gyrus (Fujita *et al.*, 55). A similar effect of morphine (6 mg/kg, iv) in the *encephale isolé* cat preparation has been reported by Matsumura *et al.* (115). Methamphetamine (9 mg/kg, iv) itself did not depress the second component of the local cortical potential nor did it enhance the morphine-induced depression.

Depending upon the species studied and dose used, morphine appears to have variable effects on specific relay nuclei of the thalamus. Fujita *et al.* (56) reported that following repetitive stimulation of nucleus ventralis posterior lateralis in cats, 8 mg/kg of morphine had no significant effect on potentials recorded in the cerebral cortex. On the other hand morphine reduced the cortical potential due to repetitive stimulation of the medial lemniscus. It had no effect on single shock responses. This would suggest that morphine increases the refractory period of neurons synapsing in this nucleus. Such an effect may be primary or secondary inasmuch as morphine in these large doses (6 mg/kg, iv) may produce hypotension. That hypotension probably is not the primary cause of this phenomenon is suggested by the data of Matsumura *et al.* (115). These investigators confirmed the fact that the augmenting response recorded from the sensory cortex to stimulation of the medial lemniscus is depressed by 6 mg/kg of morphine. They also showed that 3 mg/kg of morphine had no effect. Subsequent administration of large doses of methamphetamine (3 to 6 mg/kg) which should have caused a marked increase in blood pressure intensified the effects of morphine. Recently Deneau & Takaori (36) have demonstrated that morphine (3 and 9 mg/kg, sc) caused no change in the threshold for alerting and masticatory movements following stimulation of nucleus ventralis posterior lateralis in the monkey.

The actions of morphine upon the diffuse thalamic projection system appear to be complex. Using single shock stimuli applied to the tooth pulp of dogs immobilized with decamethonium, Heng Chin & Domino (75) observed in a few experiments that morphine prolonged the latency of potentials in nucleus median dorsalis of the thalamus which transmits impulses into the frontal lobe. This is of particular interest in view of the postulates of Wikler that the effects of morphine on pain perception in some respects re-

semble a prefrontal lobotomy. He postulated that morphine delays the transmission of impulses from the frontal lobe into nucleus median dorsalis. Heng Chin & Domino were able to show the reverse, that there was prolongation of latencies of tooth pulp impulses projected into this area. The possibility of an effect such as that hypothesized by Wikler was not ruled out. Fujita *et al.* (56) claimed that morphine in doses of 6 mg/kg given intravenously to cats decreased recruiting responses from stimulation of nucleus centralis lateralis and nucleus centrum median. However, recruiting responses from stimulation of nucleus ventralis anterior were enhanced. A similar enhancement of recruitment due to stimulation of the thalamic intralaminary system was obtained using large doses of morphine and levorphan in the unanesthetized rabbit (59). The effect was more marked after morphine than levorphan. In contrast the opposite effect was observed with the narcotic antagonist levallorphan over a wide range of doses (up to 15 mg/kg, iv). The depression of recruitment from stimulation of nucleus centrum median in cat observed by Fujita *et al.* (56) has also been reported by Matsumura *et al.* (115) in high spinal preparations. After 3 to 6 mg/kg of morphine given intravenously the recruiting response was slightly depressed. Recruitment was even more reduced after large doses (1 to 2 mg/kg, iv) of methamphetamine, although the authors doubted if this was evidence of synergism inasmuch as methamphetamine alone was very effective in depressing recruitment. In the dog there usually is a decrease in threshold and an increase in recruiting responses following small doses (0.2 to 1 mg/kg, iv) of morphine (75). Nalorphine (1 mg/kg) after morphine reduced these effects toward control. In several dogs the effects of morphine were quite complex in that some cortical areas showed recruitment of reduced amplitude while in other areas the responses were enhanced.

The mixed depressant and stimulant effects of morphine upon the hypothalamus have been reviewed by Wikler (172). Many years ago Masserman (114) showed that in the cat under light ether or postpentobarbital anesthesia the local (1 to 10 mg) or intraperitoneal injection of morphine (30 to 100 mg total) did not affect the reactivity of the cruciate cortex or the hypothalamus to electrical stimulation. However, in animals given doses of more than 60 mg total, intraperitoneally, the hypothalamic responses were limited to the duration of stimulation. Subsequently, the animals would lapse into the induced narcotic stupor. Wikler (170) has shown that in cats under urethane anesthesia the response of the nictitating membrane to hypothalamic stimulation is reduced by morphine in doses of 5 to 40 mg/kg, sc. Of particular significance was the fact that the reflex response of the nictitating membrane to sciatic nerve stimulation was even more depressed by morphine but the response to stimulation of the frontal cortex was not affected. Previous researchers have disagreed on the effects of hypothalamic lesions on morphine induced excitement in the cat [see(172)]. McCrum & Ingram (117) and McCrum (116) have shown that extensive hypothalamic lesions in cats reduce morphine-induced excitation and hyperthermia. Deneau and Takaori (36) have demonstrated

that morphine slightly increased the threshold of the posterior hypothalamus for arousal and startle in monkeys with chronically implanted electrodes. The role of the hypothalamus as an intermediary in the pituitary-adrenal activation and antidiuresis produced by morphine was reported by George & Way (63) in studies in rats with hypothalamic lesions. These investigators presented evidence that the release of antidiuretic hormone is not necessarily accompanied by a proportionate release of adrenocorticotrophic hormone by morphine, suggesting the two hormones can be released independently.

Relatively little information is available on the actions of morphine on the limbic system. Using unanesthetized rabbits Gangloff & Monnier (59) observed after intravenous injections of 20 mg/kg of morphine a generalized increase in the voltage of the electrical response to hippocampal stimulation in the sensorimotor and parietal-occipital cortex, diffusely projecting thalamic nuclei, hippocampus itself and the midbrain reticular formation. The effect was less marked after levorphan. Levallorphan, even in small doses (0.4 mg/kg, iv), decreased these diffusely evoked responses. Large doses also depressed the diffusely evoked rhinencephalic responses within 30 min of injection. One or two hours later the depression was followed by an enhanced voltage rebound. The threshold and duration of hippocampal afterdischarge was not altered by large doses of morphine (25 to 40 mg/kg), levorphan (10 mg/kg) and levallorphan (6 to 15 mg/kg) given intravenously. Deneau & Takaori (36) have shown that morphine (3 to 9 mg/kg, sc) elevates the threshold for chewing and licking in monkeys following stimulation of the amygdala. These investigators were unable to find any change in the threshold or duration of electrical afterdischarge due to stimulation of the hippocampus.

The actions of morphine upon the reticular formation appear to be quite complex. Its action upon the respiratory areas of the reticular formation has been elaborated by Hoff & Breckenridge (83). Silvestrini & Longo (149) have described a selective depression of EEG arousal to painful stimuli following 5 to 10 mg/kg, iv, of morphine. The arousal response to other sensory stimuli remained unaltered. Inasmuch as the usual order of effectiveness of stimuli in eliciting arousal is pain, proprioception, auditory and optic stimulation, the effect of morphine selectively to block pain-induced arousal would appear very significant. Furthermore, these investigators showed that after these low doses of morphine there was an increase in the EEG arousal threshold for stimulation of the anteromedial nuclei of the thalamus but not of the mesencephalic reticular formation. After large doses (10 to 25 mg/kg) of morphine the selective effect was less marked and EEG arousal to any type of stimulation was blocked. In control experiments using small amounts of pentobarbital (5 to 15 mg/kg, iv) and scopolamine (0.01 to 0.02 mg/kg, iv) EEG arousal to "sensito-sensorial" stimuli was more significantly blocked than to nociceptive stimuli. In addition, the thresholds for EEG arousal to reticular and thalamic stimulation were equally elevated.

Gangloff & Monnier (59) have also shown that large doses of morphine (20 to 40 mg/kg, iv) and levorphan (10 mg/kg, iv) depress or abolish the EEG arousal response of unanesthetized rabbits to human presence or to stimulation of the midbrain reticular formation. In contrast, levallorphan in large doses (6 to 15 mg/kg, iv) increases this effect. The spike response recorded in the sensorimotor cortex, diffusely projecting thalamic nuclei, hippocampus, and reticular formation to low-frequency (3 cps) stimulation of the midbrain reticular formation was depressed or abolished by large doses (25 mg,kg, iv) of morphine. Levorphan had a less marked and sometimes a shorter lasting effect. Large doses (6 to 20 mg/kg, iv) of levallorphan had the opposite action. Deneau & Takaori (36) have shown that morphine (3 and 9 mg/kg, sc) did not change the threshold of EEG and behavioral arousal to stimulation of the reticular formation in monkeys. Takagi *et al.* (160) have described a complex action of morphine on the descending influences of the brainstem reticular formation of the cat. After ispilateral destruction of the bulbar inhibitory area of the brainstem, morphine, in doses of 7 or 14 mg/kg, iv, enhanced both mono and polysynaptic discharges for 10 min. After destruction of the ipsilateral facilitatory areas, morphine completely diminished polysynaptic discharges and partially decreased the monosynaptic response for over one hour. It was concluded that morphine has stimulant actions on both the bulbar inhibitory and facilitatory areas but the action on the inhibitory system is predominant in intact cats. These experiments, rather complex to interpret (in view of the fact cats were used), are reminiscent of the older observations of Wikler (169) in which he suggested an action of morphine on the descending reticular substance of the midbrain of cats on the basis that the drug (5 mg/kg, iv) depressed righting reflexes and enhanced running movements or extensor tonus in acute decorticate, hypothalmic, and decerebrate animals. In high spinal cats Wikler (171) showed that 5 mg/kg of morphine, iv, enhanced monosynaptic and depressed polysynaptic discharges for several hours. These effects were consistent with older observations [see (169)] that this agent depressed the flexor reflex without affecting or slightly enhancing stretch reflexes. Larger doses of morphine (15 mg/kg) also depressed monosynaptic responses as well. After 1.5 to 2 hr, the polysynaptic discharges were enhanced. Takagi *et al.* (160) found that the level of transection of the spinal cord apparently is important with regard to the actions of morphine on spinal reflexes. In cats with low spinal transections at the level of T_1–T_2 or L_2–L_3, morphine in high dosage (14 mg/kg, iv) had negligible effects on mono- and polysynaptic potentials. In high spinal (C1-C2) animals, morphine (7 mg/kg) markedly depressed polysynaptic discharge and only slightly depressed monosynaptic potentials. These results are essentially in agreement with Wikler (171) except that in low spinal animals morphine does have a direct depressant effect on the flexor and cross-extensor reflexes. The differences observed in the effects on monosynaptic potentials are probably related to the degree of background central excitatory or inhibitory state which varies with the condition of the animal

as well as discrepancies between electrical and mechanical methods of recording spinal reflex activity. In intact, midbrain, or thalamic animals, morphine markedly depressed the polysynaptic discharges which were consistent with the hypothesis of these investigators of a descending brainstem stimulant effect of morphine which was more predominant on bulbar inhibition.

Inasmuch as morphine is an analgesic it is curious that there has not been more research on the effects of this agent on pain pathways. Fujita *et al.* (55, 56), in a series of ingenious experiments with regard to pain afferents, have concluded that in the cat morphine blocks peripheral pain afferents at the synapses of first, second, and third order neurons. Some of the experiments and the findings obtained are very difficult to interpret and therefore will not be reviewed in detail here. Again using cats Matsumura *et al.* (115) have partially confirmed and extended these observations with morphine alone and in combination with methamphetamine. Morphine is analgesic in cats and even though an atypical excitement is induced one can argue that it is valid to use cats for studying the effects of morphine on pain pathways. Nevertheless, the use of a dog or some other animal whose reaction to morphine is more similar to that of man is necessary before these observations can be generalized to other species including man. Using the tooth-pulp preparation of the immobilized dog Heng Chin & Domino (75) were unable to show that morphine in analgesic doses was able to block significantly single-shock tooth-pulp afferents in the central nervous system. On the contrary, morphine frequently enhanced evoked responses to tooth pulp afferents particularly in the reticular formation. The principal criticism of these experiments is the fact that single shock-evoked responses were used. In all probability, pain impulses are transmitted not as single discharges but rather as trains of stimuli. Therefore, one should really study the effects of morphine on trains of impulses in the pain pathways. Some *in vitro* evidence is available (see 104) that morphine probably affects the refractory period, etc. of discharging neurons.

Chlorpromazine

Chlorpromazine does not appear to have significant cortical effects per se. Preston (132) was unable to show that even massive doses of chlorpromazine (50 mg/kg, iv) had any significant depressant effects upon the isolated cortex preparation of the cat. In doses up to 8 mg/kg in high spinal cat preparations chlorpromazine had no significant effect on the transcallosal potentials recorded from the lateral gyrus [Takaori (162)]. Although chlorpromazine itself does not block the transcallosal response from the lateral gyrus it and related phenothiazines prevent catechol amine, serotonin, mescaline, and LSD-25 induced depression of this potential [Marrazzi (110)]. With many phenothiazines this effect parallels clinical potency (111). Delgado & Mihailović (34) were unable to find a significant change in the threshold of stimulation for minimal motor movements or electrical afterdischarge of areas 4 and 6 after chlorpromazine (1 mg/kg, im) in monkeys

with chronically implanted electrodes. On the other hand, Takaori & Deneau (163) found a slight elevation in threshold for electrical stimulation of the motor cortex for tonic movements after chlorpromazine (1 to 2 mg/kg, im). In doses of 5 to 10 mg/kg, iv, of chlorpromazine, Gangloff, & Monnier (60) showed in unanesthetized rabbits that chlorpromazine elevated the threshold but prolonged electrical afterdischarge to stimulation of the sensorimotor cortex. In unanesthetized high spinal cat preparations chlorpromazine (3 mg/kg, iv) depressed the second component of the local cortical response to stimulation of the lateral gyrus [Takaori (162)]. In pentobarbital anesthetized cat preparations the cortical-evoked response to stimulation of the splanchnic nerve was depressed by chlorpromazine (5 mg/kg, iv). It is of interest that both of these latter effects are similar to those produced by morphine. Evoked potentials recorded in the cortex following stimulation of the sciatic nerve are enhanced throughout the cortex following chlorpromazine in a dose of 5 mg/kg, iv (166).

Chlorpromazine does not appear to have significant effects on the specific thalamic relay nuclei. The Killams (95, 98) were unable to show any significant effect of chlorpromazine in doses up to 5 mg/kg on recovery cycles through nucleus ventralis posterior of cats in contrast to the effects of pentobarbital. Similar observations were made by Preston (132) using doses up to 50 mg/kg. Takaori (162) was able to show that chlorpromazine (3 mg/kg, iv) depressed the augmenting response recorded from the suprasylvian gyrus to repetitive stimulation of medial lemniscus of high spinal unanesthetized cat preparations. Recently Takaori & Deneau (163) have shown that in monkeys with chronically implanted electrodes chlorpromazine (1 to 2 mg/kg, im) slightly elevated the threshold for behavioral arousal to electrical stimulation of nucleus ventralis posterior lateralis. The threshold for electrical afterdischarge induced by electrical stimulation of the lateral thalamus in unanesthetized rabbits was slightly decreased by 5 to 10 mg/kg iv of chlorpromazine. The duration of afterdischarge was prolonged (60). In monkeys with chronically implanted electrodes Delgado & Mihailović (34) showed that chlorpromazine (1 mg/kg, iv) lowered the threshold to nearly one half of its original value for eliciting electrical afterdischarge due to stimulation of nucleus anterior dorsalis of the thalamus.

Chlorpromazine appears to have a slight depressant effect upon the diffuse thalamic projection system. Das *et al.* (30) reported that chlorpromazine decreased the incidence of spindles in the *cerveau isolé* cat preparation. Killam & Killam (91) reported that chlorpromazine in doses of 1 mg/kg in unanesthetized cat preparations slightly enhanced cortical recruitment, but doses in the order of 2 to 8 mg/kg slightly depressed recruiting responses. In contrast to low-frequency stimulation, high-frequency stimulation of nuclei of the diffuse thalamic projection causes EEG and behavioral arousal. Chlorpromazine (5 mg/kg, iv) appears to elevate the threshold for behavioral arousal in cats following high-frequency stimulation of this system (96). In contrast to the barbiturates, chlorpromazine appears to elevate more the

threshold for gross behavioral arousal than the threshold for EEG arousal from this system. Gangloff & Monnier (60) have reported that in the unanesthetized rabbit chlorpromazine (5 mg/kg, iv) produces an increase in the amplitude of recruiting responses to low-frequency stimulation of nuclei of the diffuse thalamic projection system.

Chlorpromazine appears to have depressant effects upon the hypothalamus. Dasgupta *et al.* (31) reported that chorpromazine (100 to 250 μg/kg, iv) suppressed sham rage of diencephalic cats. In fact, the animals showed increased sensitivity to the drug. Thiopental (2.5 mg/kg, iv) produced somewhat similar effects. Dasgupta & Werner (32) have shown that chlorpromazine (0.5 to 1.0 mg/kg, iv) produced irregular depressant effects on the blood pressure responses to stimulation of the hypothalamus and medullary vasomotor areas of intact chloralose anesthetized cats. The role of peripheral adrenergic or ganglionic blockade was not adequately evaluated; however, similar pressor responses were uniformly abolished in decorticate cats after much smaller doses of chlorpromazine (50 to 100 μg/kg, iv) suggesting increased sensitivity to the drug following decortication. Longo (106) reported that chlorpromazine depressed EEG arousal as well as the fright and flight reaction caused by stimulation of the hypothalamus in rabbits with chronically implanted electrodes. Takaori & Deneau (163) have shown that chlorpromazine (1 to 2 mg/kg, im) produces an elevation in threshold for arousal and masticatory movements from stimulation of the posterior hypothalamus. There is also evidence that chlorpromazine inhibits hypothalamo-neurohypophysial secretion (147). Barraclough (10) has reported that chlorpromazine blocks the release of pituitary gonadotrophin in rats.

A great deal has been reported on the effects of chlorpromazine on the limbic system. Preston (132) & Takagi *et al.* (161) have shown that enormous doses of chlorpromazine (40 mg/kg, iv) increased spontaneous seizure discharge in the amygdala. In contrast to this effect of toxic doses of chlorpromazine smaller doses (5 mg/kg, iv) shortened motor convulsive patterns to stimulation of either the amygdala or hippocampus when the seizure involved cortical as well as rhinencephalic structures (96). Although chlorpromazine neither altered the threshold nor changed the pattern or duration of the rhinencephalic electrical discharge it reduced the clonic component by one third. A larger dose (8 mg/kg, iv) appeared to prolong both phases of the seizure (96). Chlorpromazine in doses which markedly depress unanesthetized cats increased the threshold for limbic system afterdischarge (Killam, 97). Takagi & Ban (159) have also shown that hippocampal afterdischarge to repetitive stimulation of the precommissural fornix of high spinal cats is depressed by low doses (1 to 3 mg/kg, iv) of chlorpromazine. After 3 mg/kg, iv, the afterdischarge was completely supressed and recovered about 1 hr later. Chlorpromazine (1 to 5 mg/kg, iv) had no effect on the hippocampal potential to single shock stimuli to the fornix or its post-tetanic potentiation. It also had no effect on the evoked potential in

hippocampus to single shock stimuli to the basolateral nuclei of the amygdala. However, chlorpromazine (1 mg/kg) depressed the development of its post-tetanic potentiation. Chlorpromazine (1 to 3 mg/kg, iv) had no significant effects on the evoked potential in the hypothalamus to single shock stimulation of the hippocampus or its post-tetanic potentiation. Killam & Killam (91) have shown that chlorpromazine (2 to 8 mg/kg) depressed EEG arousal within the limbic system as indicated by slow high voltage waves; the slow waves were often replaced by fast wave activity. In monkeys with chronic electrodes Delgado & Mihailović (34) observed that chlorpromazine (1 mg/kg, im) reduced the threshold for evoked afterdischarge from stimulation of the amygdala. This effect was less marked than the lowering of threshold for evoked afterdischarge from nucleus anterior dorsalis of the thalamus. Takaori & Deneau (163) have shown that chlorpromazine (1 to 2 mg/kg, im) caused a slight increase in the threshold for emotional behavior to stimulation of the amygdala. Masticatory responses were completely blocked. Adey & Dunlop (2) studied the responsiveness of single unit discharge in the caudate nucleus and globus pallidus of the cat to sciatic nerve or amygdala stimulation before and after chlorpromazine (2 mg/kg, iv). It was observed that chlorpromazine decreased basal firing in most pallidal units. This was similar to its effects in reducing the resting firing rate of reticular units [Bradley (17)]. Adey & Dunlop noted that whereas sciatic nerve stimulation either had no effect or produced a slight decrease in the firing rate of units during the control period the same units responded with a marked increase in firing rate after chlorpromazine. A similar "release" of pallidal unit excitability was noted to amygdaloid and especially to paired lateral amygdaloid-sciatic stimuli. It was suggested that chlorpromazine effects involve an enhancement of the responsiveness of neural units in the basal ganglia and reticular formation. It is not clear whether this effect should be considered as an increase in central excitatory state in view of the fact that basal firing rates were depressed. It would be important to study other drugs such as morphine especially in the dog to determine the relationship of these phenomena to those causing chlorpromazine induced pseudo-parkinsonism.

Gangloff & Monnier (60) demonstrated in rabbits that chlorpromazine (5 to 10 mg,kg, iv) increases the threshold and duration of afterdischarge to hippocampal stimulation. There is a blockade of EEG arousal in the hippocampus from sciatic nerve stimulation following small doses of chlorpromazine given intravenously to cats [Killam & Killam (91); Killam (97)]. Takaori & Deneau (163) have shown in monkeys with chronically implanted electrodes that chlorpromazine (1 to 2 mg/kg, im) had no effect on the threshold and duration on hippocampal afterdischarge.

The brainstem reticular actions of chlorpromazine appear to be very complex. Hiebel *et al.* (79) showed that small doses of chlorpromazine depressed EEG arousal in cats with prebulbar transection. Midpontine cat preparations which showed EEG arousal to epinephrine no longer showed

epinephrine induced EEG arousal after chlorpromazine. Unna & Martin (166) also have shown that chlorpromazine blocks epinephrine induced EEG arousal. Many investigators have offered evidence pro and con on the direct effects of this agent on the brainstem arousal system. Bradley (18) and Killam & Killam (93, 95) have summarized the literature and especially their own evidence. It would appear that following low to moderate doses of chlorpromazine the threshold to sensory arousal is elevated. The threshold of EEG arousal resulting from direct stimulation of the brainstem reticular formation is not altered, but the duration of arousal may be decreased. Large doses of chlorpromazine may elevate slightly the threshold for EEG arousal. Such effects are clearly much less marked than those produced by barbiturates. Using paired equal shocks to the sciatic nerve neuronal recovery cycles in the reticular formation were determined by DeMaar *et al.* (35) and Unna & Martin (166). Two types of potentials one of short and the other of longer latency were recorded in the reticular formation in the vicinity of the red nucleus. Chlorpromazine increased the amplitude of both the short and long latency-evoked potentials. Chlorpromazine markedly depressed the recovery cycle of the long latency response. It had much less of an effect on the short latency potential. The second potential of each pair was depressed. Somewhat similar findings were made by the Killams (95). Chlorpromazine enhanced the amplitude of the first potential of each pair. It likewise prolonged the reticular neuronal recovery cycles. In contrast the amplitude of both the first and second responses of each pair were reduced by low doses (5 mg/kg, iv) of pentobarbital. The second potential was reduced more than the first. Takaori & Deneau (163) showed in monkeys with chronically implanted electrodes that chlorpromazine (1 to 2 mg/kg, im) elevated the threshold for EEG and behavioral arousal to stimulation of the reticular formation. Perhaps the most exciting findings with regard to the reticular actions of chlorpromazine are those of the Killams (93, 95) in which chlorpormazine in low doses was shown to enhance reticular inhibition of sensory input. Reticular stimulation is known to decrease the auditory evoked response in the cochlear nucleus and medial geniculate. Chlorpromazine (1 mg/kg, iv) was shown to significantly enhance reticular inhibition of auditory input. In contrast pentobarbital (10 mg/kg, im) depressed the effectiveness of the reticular formation. Rinaldi & Himwich (140) have shown that although small doses (under 6 mg/kg) of chlorpromazine depress EEG arousal in the rabbit, larger doses (over 15 mg/kg) produce EEG arousal. In studying a series of phenothiazines Himwich *et al.* (82) concluded that the facility to depress EEG arousal in the rabbit correlated with the clinical efficacy of these compounds in man.

Chlorpromazine has several important actions on the descending motor influences of the brainstem reticular formation. Its actions on the chemoreceptor trigger zone are well known [see review (129)]. Dasgupta & Werner (32) have shown that chlorpromazine depresses the medullary vasopressor response in intact chloralose anesthetized cats. The effect was much more

pronounced in decorticated animals. Gunn *et al.* (66) observed a slight increase in threshold for a pressor response to stimulation of the bulbar reticular formation and splanchnic nerve. The role of peripheral ganglionic or adrenergic blockade was not adequately evaluated. In an elegant study using cats Martin & Eades (112) studied the effects of chlorpromazine in comparison to atropine, pentobarbital and chlorpromazine sulfoxide on vasomotor and EEG arousal responses to stimulation of the midbrain reticular formation. Using data on the adrenergic potentiating as well as blocking properties of this drug especially on norepinephrine these investigators were able to show that both chlorpromazine and chlorpromazine sulfoxide decreased the excitability of the descending vasomotor system as well as the ascending activating system.

Chlorpromazine has definite effects on skeletal muscle tone. Henatsch & Ingvar (72) have shown that in cats chlorpromazine (0.5 to 2.5 mg/kg, iv) depresses *gamma* motor systems more selectively than *alpha* motor systems. The descending brainstem influences of chlorpromazine are particularly significant with regard to understanding their effects on spinal cord reflexes. Dasgupta & Werner (33) have shown that chlorpromazine depresses the crossed extensor reflex of decerebrate cats. In spinal animals the effect was much less pronounced. In intact and decerebrate cats Krivoy (103) demonstrated that chlorpromazine (0.2 to 3 mg/kg, iv) significantly depressed mono- and polysynaptic potentials. On the other hand in high spinal cat preparations Preston (132) reported that chlorpromazine even in large doses (32 mg/kg, iv) had no appreciable effects on potentiated and unpotentiated mono- and polysynaptic reflex discharge. The Russian school of investigators in a series of reports (3, 67, 89, 105) has shown the importance of the reticular formation on the spinal cord effects of chlorpromazine. Several discrepancies in the literature on the effects of chlorpromazine on spinal reflexes are understandable depending upon the preparations studied. In intact unanesthetized cat preparations Takaori (162) showed that chlorpromazine (2 mg/kg, iv) depressed polysynaptic discharges. However, in spinal cat preparations sectioned at T_2, chlorpromazine (2 mg/kg, iv) had no significant effect. Silvestrini & Maffii (150) studied a series of phenothiazines, morphine, reserpine, and hydroxyzine on the patellar (monosynaptic) and crossed extensor and linguomandibular (polysynaptic) reflexes in rabbits and cats during and after chloralose or urethane anesthesia. They were able to show that small to large doses of chlorpromazine, promazine, reserpine and hydroxyzine selectively depressed the patellar reflex of intact animals. The polysynaptic reflexes were less affected. In spinal animals the depression of the patellar reflex disappeared. On the other hand, morphine and diethazine selectively depressed the polysynaptic reflexes relatively more than the monosynaptic reflex. The effect was still present in high spinal animals. The above investigations on chlorpromazine have been extended by Hudson & Domino (85). It appears that chlorpromazine has a significant depressant effect on bulbar facilitatory areas more than bulbar

inhibitory areas. The effect is not related to potentiation of anesthesia, hypotension, etc. but represents an action of the drug per se.

Reserpine

The neural mechanisms of action of reserpine and related alkaloids have been the subject of intensive investigation. Several symposia (155, 156) have been published. In low doses reserpine appears to have negligible effects on the cerebral cortex. It has no consistent effects on the isolated cortex preparation of the dog even when administered in doses as large as 1 mg/kg, iv (42). Reserpine apparently does not affect single units in the sensory area evoked by touch stimuli in cats (145). In monkeys with chronic electrode implants reserpine did not modify the threshold of evoked afterdischarge to electrical stimulation of the precentral gyrus [Delgado & Mihailović (34)]. Similarly, Takaori & Deneau (163) have shown that reserpine (0.5 to 1.0 mg/kg, im) produced no change in motor cortical thesholds in monkeys with chronically implanted electrodes. In doses of 3 mg/kg, iv, reserpine had no effect on the transcallosal potential in high spinal cats (Takagi *et al.*, 161). On the other hand a decrease in the second component of the local cortical potential was noted in high spinal cats within 5 min following 3 mg/kg of reserpine given intravenously. In cats electrical stimulation of the anterior sigmoid gyrus produces a pressor response and contraction of the nictitating membrane which are not abolished by large doses (1 mg/kg, iv) of reserpine in contrast to the effects of ether and barbiturates [Bein (11)]. In rabbits large doses of reserpine (1.5 to 2.0 mg/kg, iv) cause an increase in the threshold without any change in duration of cortical afterdischarge [Gangloff & Monnier (60)]. A similar effect was seen with large doses (0.2 to 1.0 mg/kg, iv) of serotonin.

Reserpine in small doses (0.1 mg/kg) does not have significant effects on recovery cycles of nucleus ventralis posterior of the thalamus of the cat [King (99)]. The threshold for electrical stimulation of the lateral thalamus of the unanesthetized rabbit sufficient to produce afterdischarge is elevated by large doses (1.5 to 2.0 mg/kg) of reserpine [Gangloff & Monnier (60)]. The duration of afterdischarge is unaffected. Delgado & Mihailović (34) though have shown that reserpine given to monkeys produces a moderate decrease in the threshold of evoked afterdischarge from stimulation of nucleus anterior dorsalis of the thalamus. Takaori & Deneau (163) have observed a slight elevation in the threshold for alerting and masticatory movements to stimulation of nucleus ventralis posterior lateralis of monkeys following reserpine (0.5 to 1 mg/kg, im).

Depending upon species and dose reserpine has been reported to have no effect, a facilitant or depressant action on the diffuse thalamic projection system. For example, Gangloff & Monnier (60) have observed that reserpine in large doses (1.5 mg/kg, iv) produces a biphasic effect on cortical recruitment from stimulation of the diffuse thalamic projection system of rabbits. A transitory increase of recruiting was noted which corresponded

to an initial period of EEG slow waves. After 1 to 2 hr the recruiting response was depressed. Similar observations were made following large doses of serotonin. Kikuchi (90) has shown that reserpine in doses of 0.5 to 1.0 mg/kg, iv, either has no particular effect or produces a slight decrease in cortical recruitment from stimulation of nucleus centrum median in the unanesthetized rabbit. The effects occurred within 1 to 2 hr after reserpine administration. In cats reserpine does not affect recruitment to low frequency stimulation of nuclei of the diffuse thalamic projection system (91, 148). The Killams (96, 98) have also shown reserpine in doses of .1 mg/kg given intravenously to cats had no effect on the threshold of EEG or gross behavioral arousal in cats to high-frequency stimulation of nuclei of the diffuse thalamic projection system.

The hypothalamic actions of reserpine are complex. The early investigators hypothesized that reserpine exerted its actions primarily through a depressant action on the hypothalamus. In view of our present knowledge of the relatively high content of catechol amines and serotonin in this area this still seems to be a logical site of reserpine action. Gaunt *et al.* (62) were unable to show that small doses of reserpine cause endocrine manifestations as a result of hypothalamic depression. After large doses of reserpine, pituitary gonadotropin is blocked in rats [Barraclough (9)]. This is presumably via a hypothalamic action of reserpine. Miline *et al.* (119) have studied in detail the actions of reserpine on the hypothalamic-hypophyseal system. They report that the actions are quite complex involving stimulation of the supra-optic and paraventricular nuclei, adrenotropic with dissociation of gonadotropic activity. Thyrotropic activity was depressed. In curarized rabbits, Longo & Napolitano (107) and Bovet & Longo (16) have shown that reserpine in doses of 0.5 to 7 mg/kg, iv caused initial EEG arousal and a secondary depressant phase characterized by slow waves and diminished response to external stimuli. In rabbits with chronically implanted electrodes in the hypothalamus similar findings were noted. After an initial excitatory phase and during the period of depression the usual fright and flight reactions of the rabbit to stimulation of the hypothalamus were depressed. Schneider (144) has pointed out that reserpine (.1 to 1.0 mg/kg) in cats does not decrease the blood pressure response to stimulation of the hypothalamus. In sham rage cat preparations, reserpine (0.5 to 1.0 mg/kg, iv) completely inactivates the rage picture. Interestingly, reserpine-induced miosis so typical of an intact animal was not observed. However, in some animals the pupil tended to constrict. This would indicate that some structure anterior to and above the hypothalamus needs to be present to allow characteristic reserpine miosis, although Hamel & Kaelber (68) were able to show that in three cats in which the hypothalamus posterior to the optic chiasm was intact reserpine produced pupillary constriction. This positive evidence therefore suggests a hypothalamic effect of reserpine. However, EEG recordings from this area did not support (or rule out) this consideration. Investigations of the effect of reserpine on the hypothalamic pressor

response are complicated by the fact that the responsiveness to norepinephrine is increased. By comparing pressor responses to injections of norephinephrine and hypothalamic stimulation Harrison & Goth (69) were able to show that reserpine (50 to 200 μg/kg) augmented the hypothalamic pressor response less than was expected when compared to the augmentation of the norepinephrine response. On the other hand, Bhargava & Borison (14) could demonstrate hypotension and depression of medullary reticular responses by reserpine even in midcollicular decerebrate cats. These investigators felt the hypothalamus was excluded as a predominant site of the hypotensive action. Using cats immobilized with gallamine Gunn *et al.* (66) were unable to show any effect of reserpine (0.1 to 1.0 mg/kg, iv) on the threshold for a pressor response to stimulation of the brainstem reticular vasomotor areas. In bilaterally vagotomized barbiturate anesthetized cats Horwitz *et al.* (84) were able to show that reserpine (0.5 mg/kg, iv) depressed both hypothalamic as well as medullary vasomotor pressor responses. In addition, the depressor responses were also reduced. The reasons for these discrepancies among various researchers is not obvious. Takaori & Deneau (163) have shown that reserpine (0.5 to 1.0 mg/kg, im) produces a slight elevation in the threshold for arousal and startle from stimulation of the hypothalamus of monkeys.

The actions of reserpine upon the limbic system vary depending upon dose, species, and duration following reserpine administration. Monroe *et al.* (125) did not observe any increase in spontaneous seizure discharge in the amygdala and hippocampus of chronic schizophrenic patients after acute (2.5 to 10 mg, iv) as well as prior chronic administration of this agent. In monkeys with chronic electrodes reserpine had no effect on the threshold for evoked afterdischarge from. stimulation of the amygdaloid nucleus [Delgado & Mihailović (34)]. MacLean *et al.* (109) described slow wave rhythms of 2.5 to 3.5 cps in the hippocampus following reserpine administration to cats. These investigators pointed out that similar hippocampal slow waves were seen following administration of diethyl ether. Killam *et al.* (96) showed that small doses of reserpine did not change the threshold but increased the duration of limbic system afterdischarge. Following chronic administration of reserpine the threshold decreased and spontaneous electrical seizures were noted in the hippocampus which projected to other areas of the brain (92). Sigg & Schneider (148) showed that large doses (0.5 to 1.0 mg/kg) of reserpine increased the duration of afterdischarge from stimulation of the amygdala or hippocampus in high spinal cat preparations. Both amphetamine, methylphenidate and intense electrical stimulation of the brainstem reticular formation decreased the duration of evoked limbic seizures in normal as well as reserpine treated animals. Using unanesthetized rabbits Gangloff & Monnier (60) have also shown that reserpine in large doses slightly prolongs hippocampal afterdischarge, but does not affect the threshold. In contrast to the above groups of workers Takagi & Ban (159) were unable to show any consistent effects of 0.5 to 1.0 mg/kg of reserpine

on the threshold and duration of hippocampal seizures in high spinal cats within 4 hr after acute administration. In doses of 1.0 mg/kg, iv, reserpine had no effect on the evoked response in the hippocampus to single shock stimulation of the fornix or its post-tetanic potentiation. It also had no effect on the evoked potential in the hypothalamus to single shock stimulation of the hippocampus or its potentiation. Although reserpine had no effect on the evoked potential in the hippocampus to single shock stimulation of the basolateral nuclei of the amygdala, it did depress its post-tetanic potentiation. Takaori & Deneau (163) did not observe any change in the threshold for a complex of behavioral effects to stimulation of the amygdala or any change in the threshold and duration of afterdischarge to stimulation of the hippocampus following 0.5 to 1.0 mg/kg of reserpine in monkeys with chronically implanted electrodes. The 3.5 to 4 cps hippocampal rhythms observed by MacLean *et al.* (109) were not observed by Hamel & Kaelber (68). These investigators were able to show that reserpine (0.5 to 1.0 mg/kg ip) in cats caused a decrease in threshold and a variable increase in hippocampal afterdischarge. In only 2 of 13 animals spontaneous seizure discharges were observed in the hippocampus. Hamel & Kaelber disagreed with the Killams on the relative frequency of spontaneous seizure discharge which the latter investigators recorded in both animals studied. Similarly Sigg & Schneider (148) pointed out a much lower incidence of spontaneous seizure discharge in cats. The significance of a facilitating effect of reserpine on limbic seizure discharge is not certain. It is well known from the work of Jung (87) that the hippocampus is especially prone to seizure discharge. Certainly seizure discharge of this system does not appear to be correlated with tranquilization. The facilitating effect of reserpine does not appear to be due to the initial release of catechol amines inasmuch as chronic reserpine medication apparently is more effective in enhancing seizure susceptibility. Presumably with chronic treatment catecholamine levels in the brain would be minimal.

The actions of reserpine upon the brainstem reticular formation also depend very much upon the species, dose and duration of treatment. For example, the rabbit may show no effect, a decrease or an increase in EEG arousal threshold. With doses up to 0.5 mg/kg, iv of reserpine Rinaldi & Himwich (139) showed that reserpine had no significant effect on EEG arousal. On the other hand, large doses in the order of 1.0 to 2 mg/kg given intravenously decreased the threshold for EEG arousal and frequently caused spontaneous EEG arousal. Gangloff & Monnier (60) have pointed out that large doses of reserpine blocked EEG arousal reaction to human presence in 1 to 2 hr after administration. EEG arousal elicited by stimulation of the midbrain reticular formation was decreased or abolished 1 hr after reserpine administration. Following reserpine the spike response to low frequency stimulation of the midbrain reticular formation was decreased in the cerebral cortex and thalamus, but not in the hippocampus and reticular formation [Gangloff & Monnier (60)]. Kikuchi (90) has observed a decrease

in EEG arousal 6 to 8 hr after the administration of reserpine in doses of 0.5 to 1 mg/kg given intravenously to unanesthetized rabbits. In cats, doses of 0.1 mg/kg of reserpine given intravenously had no particular effect on EEG arousal (91, 96). Takagi *et al.* (161) saw no change in the threshold for EEG arousal in cats following doses of 3 mg/kg intravenously of reserpine. Hamel & Kaelber (68) have pointed out that reserpine appears to have no direct EEG arousal effects in the cat although some cortical arousal may be evident from indirect peripheral afferent stimulation as a result of increased visceral motility. Takaori & Deneau (163) have shown in monkeys that reserpine (0.5 to 1.0 mg/kg, im) elevated the threshold to stimulation of the reticular formation for EEG and behavioral arousal.

In large doses (5 mg/kg, iv) reserpine was reported to increase the patellar reflex of high spinal cat preparations. These effects persisted for approximately 1 to 2 hr (145). Schneider *et al.* (145) also showed that similar large doses of reserpine increased monosynaptic potentials in the spinal cord of cats. An inconsistent increase in polysynaptic discharge was observed. Esplin & Heaton (47), however, were unable to find that large doses (up to 10 mg/kg, iv) of reserpine had any significant facilitatory effect upon reflex excitability of the spinal cord in either spinal or decerebrate cats. Synaptic recovery cycles, response to repetitive stimulation, and direct inhibition of the monosynaptic pathways were unaffected after this agent. However, post-tetanic potentiation in the monosynaptic pathway was markedly reduced by large doeses of reserpine. This effect was seen in both spinal and decerebrate cats. It was attributed to an action of reserpine rather than its vehicle. Krivoy (103) reported that reserpine (5 mg/kg) depressed the mono-and polysynaptic spinal cord potentials in intact and decerebrate cats. Somewhat similar findings were made by Silvestrini & Maffii (150) on the patellar reflex in intact chloralose and urethane-anesthetized rabbits and cats following 0.1 to 1.5 mg/kg of reserpine. The crossed extensor reflex was almost unaffected. Reserpine inconsistently depressed the linguomandibular reflex. Reserpine had no effect in spinal animals, nor does it transiently enhance the patellar reflex. Extensive vehicle controls were not reported.

Conclusions

All forms of data reduction invariably lose certain information. Similarly, when a reviewer attempts to summarize and present a logical story some data, perhaps ultimately very important, are lost from the distillate. Nevertheless, by forming definite conclusions a pattern of possible sites of drug action within the central nervous system may emerge which is meaningful. Perhaps the pattern formed may not be entirely correct. Yet, it does appear essential that a model of central drug action be presented even though our total knowledge of cerebral mechanisms is rather embryonic. Although neuroanatomists have long known that the calvarium is not filled with a homogenous "cotton," it is comforting to note that neuropharmaco-

logical techniques provide data that reflect the known anatomical complexity of the central nervous system. Not all integrative areas of the brain react alike to various central nervous system depressants. In fact, the differences in drug action are marked. Drugs may act predominantly on afferent, integrative, or efferent mechanisms.

In attempting to present an overall picture of site of drug action which may be applicable for a variety of species including man, the reviewer has chosen to group the data on the basis of a small or large dose effect. The criteria of what is a small or large dose of any drug, of course, vary widely. In general the rule followed was that for any given species doses which cause minimal but obvious central nervous system effects were considered small, while those producing marked gross central nervous system effects were considered large. Any discussion lacking the concept of the dose administered tends to be meaningless. In Table I are listed most of the central nervous system depressants reviewed, and some of the more important integrative areas of the central nervous system. The absence of the basal ganglia and cerebellum is quite evident. Although data on effects of drugs on these systems have been published the total amount available appears to be insufficient to warrant inclusion at this time. An arrow pointing upward indicates stimulation of the neuronal area involved, and an arrow pointing downward depression. Although the words "stimulation" and "depression" are widely used they are extremely poor terms inasmuch as ultimate neuronal or synaptic mechanisms are not specified. One may see stimulation by depression of an inhibitory system and *vice versa* (see Grundfest, 64). Nevertheless, the terms do provide a useful means of grossly describing a phenomenon, and are used only in this sense.

Barbiturates.—As summarized in Table I, barbiturates affect many areas of the central nervous system. Small doses depress the cerebral cortex, thalamus, hypothalamus, limbic system, brainstem reticular formation, and spinal cord. Probably because of depression of the ascending reticular formation a release phenomenon results in a decrease in the threshold for recruitment from slow frequency stimulation of the diffuse thalamic projection system and facilitation of the potential amplitude through specific relay nuclei. A similar phenomenon probably accounts for the occasional reports of a cortical stimulant effect. In small doses barbiturates appear to depress primarily polysynaptic pathways in the spinal cord. Large anesthetic doses of barbiturates have widespread depressant effects throughout the central nervous system. Neuronal recovery times in the thalamus and probably other structures are markedly prolonged. Both mono- and polysynaptic pathways in the spinal cord are depressed.

Meprobamate.—Although the spectrum of activity of meprobamate appears somewhat similar to that of the barbiturates several important differences may be noted as illustrated in Table I. In general meprobamate is much less potent. Low doses of meprobamate in man produce EEG fast waves primarily in parietal association areas as opposed to the barbiturates

TABLE I

SITES OF ACTION OF SOME CENTRAL NERVOUS SYSTEM DEPRESSANTS

CNS Depressant	Site in CNS													
	Cerebral Cortex		Thalamus				Hypothalamus		Limbic System		Brainstem Reticular Formation		Spinal Cord	
			SRN		DPTN									
	SD	LD	SD	LD	SD	LD	SD	LD	SD	LD	SD	LD	SD	LD
Barbiturates	↓, ↑ (R)	↓ ↓	↓, ↑ (R)	↓	↓, ↑ (R)	↓	↓	↓ ↓	↓	↓ ↓	↓	↓ ↓	↓ P	↓ ↓ M, ↓ ↓ P
Meprobamate	—	↓	sl. ↓	↓	—, ↓ (I)	↓	sl. ↓	↓	sl. ↓	↓	—	↓	↓ P	↓ M, ↓ ↓ P
Morphine	—	↓ ↑	—	↓	↓, ↑ (R)	↓ ↑ (R)	↓, ↑	↓ ↓	—, ↓	↓	sl. ↓ ↑	↓ ↓	↓ P*	↓ ↑
Chlorpromazine	—	↓, ↑ (I)	—	↓, ↑	↓, ↑ (R)	↓	↓	↓ ↓	—, ↑, ↓	↑	sl. ↓, ↑	↓ ↑	—	—
Reserpine	—	—, sl. ↓	—	sl. ↓	—	↑ ↓ (I)	↓ ↑	↓ ↑	—, sl. ↑	↑	—	↑, ↓	—	sl. ↑ ↓

sl. ↑ —slight stimulation
↑ —definite stimulation
sl. ↓ —slight depression
↓ —definite depression
↓ ↓ —marked depression
(R)—release phenomenon probably due to reticular depression
(I) —Indirect effect via reticular formation or unknown

SRN —specific relay nuclei of thalamus
DPNT—diffusely projecting thalamic nuclei
SD —small dose causing some CNS effects
LD —large dose causing marked CNS effects
M —monosynaptic reflexes
P —polysynaptic reflexes
* —Some short polysynaptic pathways stimulated

which produce similar fast wave activity more in frontal association areas. Insufficient animal data are available as to whether low doses of meprobamate produce any significant cortical depression. There appears to be agreement in the literature that small doses of meprobamate tend to produce preferential EEG slowing and hence evidence of depression in specific relay nuclei and other areas of the thalamus. The diffuse thalamic projection system may be similarly involved. Recruiting responses may be unaffected, slightly enhanced or depressed secondary to an action on the brainstem reticular formation. Low doses of meprobamate having no depressant effect on the brainstem reticular formation appear to slightly depress the hypothalamus and limbic system. Small doses of meprobamate have minor depressant effects on polysynaptic discharge in the spinal cord. Larger doses of meprobamate produce definite depression of the cerebral cortex, hypothalamus, limbic system and reticular formation. Likewise, there is depression of polysynaptic potentials in the spinal cord with a slight depression of monosynaptic potentials. No evidence for a unique skeletal muscle relaxant effect has been demonstrated that is not shared with some of the barbiturates. Perhaps the most important action of meprobamate in doses producing depression of limbic and hypothalamic structures is that it appears to have less of an effect on arousal mechanisms than most barbiturates. Large doses of meprobamate have depressant effects on recurrent facilitation in the spinal cord. Recurrent inhibition appears to be enhanced. Although similar effects are seen with barbiturates the latter appear to be more depressant to monosynaptic reflexes.

Methaminodiazepoxide.—Obviously in view of the very limited amount of data available on the neuropharmacology of this compound, it is entirely premature to suggest any definitive sites of action within the central nervous system. On the basis of data available it appears that this agent causes depression of limbic system afterdischarge and polysynaptic reflexes in the spinal cord in doses below those necessary to produce depression of the brainstem reticular formation. This would suggest a spectrum of central nervous system activity somewhat different from meprobamate and the barbiturates. This is especially true with low doses of methaminodiazepoxide. On the other hand large doses of this compound probably produce diffuse depression. Further evidence to support these notions is obviously necessary.

Morphine.—The actions of morphine are complicated by very marked species variation. Because of this, generalizations are very difficult to make that apply to several species. Nevertheless, an attempt has been made as illustrated in Table I to summarize some of the more important actions of morphine. In low to moderate doses morphine has negligible actions upon the cerebral cortex. Inasmuch as augmenting responses appear to be depressed in some species and enhanced in others, most of the specific relay nuclei do not appear to be a crucial site of action of morphine particularly in low dosage. Morphine may prolong the latency of tooth pulp afferents into nucleus median dorsalis which projects into the frontal lobe. In general

it tends to increase recruiting responses from stimulation of the diffuse thalamic projection system. Apparently this is partly a release phenomenon due to slight depression of the brainstem reticular formation. Its effects on recruiting responses appear to be complex. Not all nuclei of the diffuse thalamic projection system appear to be similarly affected. The hypothalamic effects of morphine appear to be mixed with some evidence of depression as well as stimulation. In low dosage, morphine either has negligible or a slight depressant effect on the limbic system. The drug appears to have a selective effect on the reticular formation in depressing pain induced arousal. Evoked responses within the reticular formation appear to be slightly enhanced perhaps as a secondary release phenomenon. The actions of morphine upon the spinal cord are complicated by a descending brainstem effect. In intact animals morphine in low dosage depresses polysynaptic discharge. In very low spinal cats morphine appears to have negligible effects. With high dosage, morphine has a pattern of mixed stimulant and depressant effects especially at cerebral cortical, thalamic and spinal cord levels (see Table I). Large doses of morphine appear to depress the hypothalamus and limbic system. In general large doses of morphine depress the brainstem reticular formation as evidenced by depression of arousal and respiration. The actions of morphine upon the spinal cord are in part complicated by a higher brainstem reticular stimulant effect. In high spinal animals direct mixed depressant and stimulant actions are observed.

Chlorpromazine.—In low dosage this agent appears to have negligible effects on the cerebral cortex and specific relay nuclei of the thalamus. Recruiting responses may be slightly enhanced perhaps as a release phenomenon although others have reported depression of the diffuse thalamic projection system. Prolongation of afterdischarge and a lowering of threshold has also been observed in this system. Chlorpromazine in low doses appears to have a slight depressant effect upon the hypothalamus and limbic system. In some animal species a slight stimulant effect on the limbic system may also be observed. In low dosage, chlorpromazine appears to have slight depressant effects on the brainstem reticular formation as evidenced by depression of the chemoreceptor trigger zone, possible depression of vasomotor activity and decreased arousal to sensory stimuli. An interesting and apparently unique effect of chlorpromazine is that of increasing the inhibitory effects of the activating system on sensory input. Recovery times of reticular neurons appear to be prolonged. The direct actions of chlorpromazine on the spinal cord are minimal. However, in intact animals there is depression of mono-and polysynaptic discharge which is mediated through a higher brainstem influence. Chlorpromazine in low doses depresses bulbar facilitatory area to a greater extent than bulbar inhibitory areas. As a result the descending influences of bulbar inhibition tend to predominate in chlorpromazine treated animals. Large doses of chlorpromazine produce very mild mixed depressant and stimulant actions on the cerebral cortex. Similarly there appears to be a slight depression or enhancement of activity

of specific relay nuclei. Depression of the diffuse thalamic projection system is observed. Large doses of chlorpromazine have a depressant effect upon the hypothalamus. In very large toxic doses, chlorpromazine appears to have a direct stimulant effect upon the limbic system. This does not appear to be essential for its tranquilizing properties, but is related to the toxic manifestations of this drug. The actions of chlorpromazine upon the brain stem reticular formation in large dosage appear to be a mixture of depression and stimulation. Even massive doses of chlorpromazine have negligible effects upon spinal cord reflexes in spinal animals. The effects in intact animals appear to be mediated by a higher central influence through the descending brainstem reticular formation.

Reserpine.—It would appear that in small doses reserpine has negligible effects on the cerebral cortex, specific relay nuclei of the thalamus, brainstem reticular formation, and spinal cord as is illustrated in Table I. Reserpine appears to have a mild depressant-stimulant effect upon the hypothalamus. In low dosage reserpine appears to have either no effect or a slight facilitant effect on the limbic system. In large dosage reserpine has either no significant action or a slight depressant effect on the cerebral cortex. It may produce slight depression of the thalamus. A transitory increase in recruiting responses can be observed which may be related to a release phenomenon due to transient depression of the brainstem reticular formation. Particularly in rodents where stimulation of the brainstem reticular formation is observed there may be a depression of recruiting responses elicited from the diffuse thalamus projection system following large doses of reserpine. Large doses of reserpine have a mixed depressant and stimulant effect on the hypothalamus. Reserpine in large dosage also facilitates discharge of the limbic system. This does not appear to be a necessary concomitant of its tranquilizing effects. Such stimulation of the limbic system apparently occurs more on chronic administration and may lead to convulsions which originate in this system.

As described above large doses of reserpine also stimulate the brainstem arousal system, especially in rodents. In other species no marked arousal effects are observed on the basis of a direct reticular action of reserpine. The drug appears to have negligible spinal cord actions unless large doses are used. Early reports suggesting an increase in monosynaptic reflexes may be on the basis of vehicle effects. Subsequent reports tend to suggest a depressant effect if any. Some of the depressant effects may be related to a higher action on the brainstem reticular formation.

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