THE EFFECTS OF CATECHOLAMINES ON THE CENTRAL NERVOUS SYSTEM

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I. INTRODUCTION

Around the turn of this century, a German physician, impressed by the recent discovery that epinephrine improved local cocaine anesthesia, was led to try the same combination as a spinal anesthetic. When this combination again seemed superior to cocaine alone, he investigated the effect further, including the administration of epinephrine without cocaine. He found that while epinephrine lacked local anesthetic properties altogether, it produced excellent analgesia intraspinally. He then injected it into the carotid circulation of conscious cats and observed that they became almost totally insensitive to pain. Moreover, although sleepy, they still reacted to auditory, visual, and tactile stimuli. He reasoned that this relative preservation of the so-called higher functions eliminated general cerebral ischemia as a mechanism of action and concluded "Nicht nur auf das Blutgefässystem, sondern auch auf spezifische Nervenorgane, die Organe der Schmerzempfindung müssen wir also der Nebennierensubstanz eine Wirkung zuerkennen" (269). More than half a century has now elapsed since Professor Weber's remarkable observations. Equally surprising, however, is the fact that while it has been confirmed repeatedly, no satisfactory explanation for this important finding has ever been provided and no practical use made of it; instead we are confronted by the apparent paradox that epinephrine, according to popular opinion at any rate, is virtually synonymous with stimulation, excitement or exhilaration.

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Over the years, scientific observations on the central actions of the catecholamines have accumulated rather slowly—principally as separate observations rather than any unified series of studies; indeed this is still the case. However, in view of the rapid strides being made currently in neurophysiology and its related disciplines neuropharmacology and neuroendocrinology, it has become increasingly desirable to understand what actions, if any, such substances as epinephrine and norepinephrine have upon the central nervous system, and probably more important, what inferences we may draw from such knowledge about their normal role in nervous function or their possible culpability in brain disease. No review of this sort seems to have been attempted in the past; moreover, considering current interest in the field, it is safe to predict that such a subject will become unwieldy before too many more years.

The present paper, without attempting exhaustive coverage, will touch upon the major aspects of catecholamine action upon the central nervous system from both a neurophysiological and behavioral standpoint, in an attempt to gather together much of the disparate and seemingly unrelated data in the literature. Where possible, some effort will be made to suggest unifying principles even when the proof for these remains lacking, and as much emphasis will be placed upon certain theoretical hypotheses as upon observations which still defy analysis or explanation. It would be entirely too optimistic to expect any complete or coherent picture to emerge. Nonetheless, a beginning has been made and bears examination; moreover, such a survey can point out important gaps in our present knowledge and suggest profitable lines of research for the future.

It will not be possible to go into the problem of the central control of catecholamine secretion, nor is it feasible to consider, except briefly, the host of pharmacologic agents with real or fancied resemblances to epinephrine which have attracted so much attention recently because of a possible relation to mental disease or the action of tranquilizing drugs. Furthermore, little or no reference can be made to the biochemical effects of these amines upon brain tissue either *in vivo* or *in vitro*.

Throughout this paper, considerable emphasis will be placed upon such matters as dosage, mode of administration, and the properties of the preparation being tested, especially anesthesia. For it is obvious that an effect which can be obtained with 1 μg/kg or less of norepinephrine intravenously need not bear any relation to a different phenomenon requiring more than 100 μg directly into the carotid artery to become apparent. To compare them, when the brain concentration may differ by a factor of 1000 or more, could be quite misleading. Some of the reports to be covered offer seemingly contradictory results; these can sometimes be resolved by a comparison of methods, species differences, or dosage.

Finally, it is obvious that the central nervous system is not a single organ, but a large collection of information processing devices and communications mechanisms differing in structure, function, blood supply and chemical composition. It is too much to ask that the action of potent pharmacologic agents like the catecholamines will follow any simple or consistent pattern, for their central action is the sum of their actions upon each separate affectable brain

mechanism; of these there must be a great number, some recognized and fewer understood.

II. PRELIMINARY CONSIDERATIONS

A. Transmission at peripheral synapses

1. Autonomic. There are sufficient pharmacologic differences between various peripheral synapses to make one wary of comparisons—all the more of comparisons between peripheral and central synapses. Nonetheless, considerable study has been devoted to the effects of epinephrine on peripheral sympathetic synapses, and these may be examined briefly before going on to a consideration of its central effects. In 1939, Marrazzi (154) showed that epinephrine had a depressant action upon transmission in the superior cervical sympathetic ganglion of the anesthetized cat. The effects were determined by measuring the height of the postsynaptic spike in response to presynaptic electrical stimulation at 2/sec. Doses of 10 to 250 μg of epinephrine intravenously caused a diminution or even a disappearance of the postsynaptic spike, and since the effect could not be duplicated by anoxia it was assumed that the action of epinephrine was direct and not secondary to local ischemia. He showed also that stimulation of the animal's own adrenals by the peripheral splanchnics had the same effect (155), suggesting that the response was within the physiological range. This was confirmed by Posternak and Larrabee (199), in whose experiments adrenal discharge was produced by clamping the aorta, and transmission studied in the stellate ganglion. Marrazzi also proposed that this peripheral inhibition of sympathetic ganglia by epinephrine might normally act to prevent excessive sympathetic activity in certain situations (153). Subsequently he extended his observations to other sympathetic (paravertebral and mesenteric) and parasympathetic (ciliary) ganglia which also showed depression from epinephrine. In certain of the preparations the presence of nonsynapsing fibers made it possible to demonstrate that the action of epinephrine was only at the synapse itself (156, 260, 261).

Subsequent work has borne out these results. Lundberg (140), using a similar experimental setup with single shocks for stimuli, found depression from as little as 1 μg of epinephrine intravenously and noted that norepinephrine also produced depression but was only one-quarter as effective. His studies of demarcation potentials suggested that the synaptic blockade produced by epinephrine was not accompanied by de- or hyperpolarization, but was more like that of curare. Likewise, Matthews (166) observed depression (but never complete block) from as little as 0.3 to 0.7 μg/kg of epinephrine in the unanesthetized decerebrate cat; he found that norepinephrine was only one-third as effective and that isoproterenol had the opposite effect, augmentation. By careful analysis of the postsynaptic wave form, he showed that the fall in spike height was not due to temporal dispersion, and that the depressant action of epinephrine affected only two of the three sets of postsynaptic fibers leaving the ganglion (presumably those destined for the nictitating membrane and blood

vessels, but not those going to glands). All three were quite susceptible to depression by barbiturates, however. Neither of the above authors observed augmentation from epinephrine or norepinephrine in any dose.

Bülbring and Burn (37) employed a different experimental setup and obtained somewhat different results. Using separate perfusion of the hind limb and the abdominal sympathetic ganglia, they observed an increase in vasoconstriction of the limb to a given electrical stimulation of the sympathetics when small amounts of epinephrine were added to the ganglion perfusate; larger doses, however, produced depression instead. Subsequently, Bülbring (34) observed the effects of epinephrine on the perfused superior cervical sympathetic ganglion, using preganglionic electric stimulation and recording the contractions of the nictitating membrane. Adding epinephrine in a concentration of $1:10^6$ increased the responses of the nictitating membrane; again, larger doses had the opposite effect.

In 1947, Marrazzi (165) attempted to reconcile the two sets of results. In some instances, particularly with larger doses, he reported observing facilitation following the inhibition regularly seen after epinephrine. He felt this was nonspecific, however, since it was seen after ischemia also and suggested that the failure of the preceding authors to observe inhibition from smaller doses was due to the conditions of their experiment, in particular the intermittency or delay of the test-object response. More recently, Malméjac (147) in a series of cross-perfusion experiments, has confirmed the observation that small doses of epinephrine (infusion of 0.5 to 4 μg/kg per min) tend to enhance the response of sympathetic ganglia—in this case measured as the release of epinephrine and norepinephrine from the adrenal medulla from stimulation of the splanchnic nerves—while larger doses (infusions of 12 to 15 μg/kg per min) decrease the response.

Both Bülbring and Burn, and Malméjac also observed an increase in the response to injected acetylcholine following suitable doses of epinephrine. Using the perfused superior cervical ganglion and recording contractions of the nictitating membrane, Konzett (127) observed regular augmentation of the responses to acetylcholine injection by addition of epinephrine, which was effective in doses of 0.01 to 5 μg. Smaller doses tended to show tachyphylaxis, but larger doses were not observed to cause depression. Comparing these with other catechols as well as phenyl derivatives, he concluded that the ganglionic responses resembled those of the beta adrenotropic receptors of Ahlquist (2). He observed that sympathicolytic agents (ergot derivatives, Dibenamine) did not prevent this augmenting effect of epinephrine on the response to acetylcholine, and it may be noted that Matthews failed to block the effect of epinephrine and norepinephrine with Dibenzyline in his preparation. Subsequently, Kewitz and Reinert (123, 124) have compared the effect of epinephrine on the perfused ganglion in response to both acetylcholine injection and preganglionic nerve stimulation, using the contractions of the nictitating membrane as an indicator. They found that in general epinephrine augments the acetylcholine-induced response,

but diminishes the response to nerve stimulation. Kewitz has since cited this discrepancy as a reason for doubting that acetylcholine is the or at least the only physiological transmitter substance at this particular synapse (122).

It is quite obvious that the last word has not yet been said on this important subject. Results will vary depending on whether the stimulus is electrical excitation of the preganglionic nerve (where the rate of stimulation is important), or the injection of acetylcholine into the ganglion perfusate; or whether the indicator used is postganglionic potentiation or the actual response of an effector organ such as the nictitating membrane, adrenal medulla, vasoconstrictor nerves, etc.

In summary, there seems to be general agreement that both epinephrine and norepinephrine will diminish the postganglionic potentials of sympathetic fibers in relatively physiological doses. This depression must be distinguished from that already present from the barbiturates used in most of these experiments. Augmentation of these potentials has never been observed. Using an actual effector organ as an indicator, various investigators have shown augmentation from small doses of epinephrine and depression from larger doses. Finally, using acetylcholine instead of preganglionic nerve stimulation to excite the ganglion and an effector organ as an indicator, augmentation seems to be the rule for both epinephrine and norepinephrine. These actions of epinephrine and norepinephrine appear to be unaffected by adrenergic blocking agents.

In further work in this field, particular attention should be paid to the simultaneous comparison of both postganglionic potentials and the response of the innervated effector organ, to see to what degree they correspond. Moreover, more use should be made of perfusions at a constant rate, or subcutaneous injections, rather than the single intravenous injection technique where the drug concentration is always rapidly changing, especially since most of the observations on indicators are of the discontinuous sort.

One might well inquire whether the effects of epinephrine and norepinephrine upon these peripheral ganglia are particularly relevant, since the preganglionic fibers themselves are presumably cholinergic. Attention has been called to the presence of chromaffin cells in both sympathetic (34) and parasympathetic (261) ganglia, and the suggestion made that these cells might release adrenergic substances into the synaptic regions of the ganglion. Moreover, the release into the ganglion perfusate of an epinephrine-like substance upon stimulation has been reported (34). It seems possible that such a mechanism might serve to modulate the cholinergic transmission normally taking place, although whether in the direction of facilitation or depression, or both, is still an open question. If nothing else, the foregoing data reveal the complexity of the pharmacology of this relatively simple synapse and furnish us with an ample warning of the much greater difficulties to be expected in understanding the effects of adrenergic substances upon central mechanisms.

2. Sensory and motor. While it is beyond the scope of this review to take up all the effects of epinephrine and its congeners upon peripheral sensory and motor mechanisms, the subject should be mentioned if only to remind the reader that

some of the effects of these substances now assumed to be central may turn out to be peripheral instead. For example, as will be taken up in the section on the spinal cord (III, A), many of the earlier experiments on the effects of epinephrine upon spinal cord activity were performed in lightly anesthetized but otherwise intact preparations; a wide variety of complex and often contradictory results was obtained. In one of the most recent studies of this problem, however, great pains were taken to eliminate all possible effects of epinephrine except those originating in the cord itself, with the result that it was seriously questioned that there was any effect of epinephrine demonstrable upon the spinal cord at all (53).

In a recent paper, Loewenstein (134) has reported the interesting observation that stimulation of the peripheral sympathetics or the application of epinephrine or norepinephrine to the skin of a frog will lower the threshold and slow the adaptation of tactile receptors, as determined by electrical recording of their output. These agents may even provoke "spontaneous" discharge, provided the amount is sufficient and the skin under some stretch. The author speculates that the sympathetic neurohumors act by modifying the response characteristics of the receptor organ, in particular the time-constant of its generator potential. Since no true synapse is involved, and since the effects of epinephrine and norepinephrine appear to modulate rather than stimulate the receptor mechanism, he proposed the term "modulapse." While work of this sort does not appear to have been done on mammals, doubtless it soon will be, and the possibility of modulation by epinephrine and norepinephrine of sensory input from a variety of receptors should always be kept in mind.

In a review on epinephrine and its relation to acetylcholine in the nervous system, Burn (39) called attention to the peripheral potentiation by epinephrine of acetylcholine stimulation of mammalian striated muscle, a phenomenon related to the classical Orbeli effect in which stimulation of the sympathetic fibers will increase the contractile tension of the fatigued frog muscle. In a further analysis of this effect Hutter and Loewenstein (109) find that the increase in tension is accompanied by an increase in the end-plate potential, so that in the frog it seems to act through the mechanism of the myoneural junction. In mammals, on the other hand, there is no evidence that epinephrine works by lifting a partial neuromuscular block; instead it appears to affect the muscular contraction directly, including an increase in the duration of the muscle action potential (33). In a recent series of studies, Goffart (76) finds that epinephrine can produce a 5 to 20% increase in the contractile force even in nonfatigued mammalian skeletal muscle. The effect appears to be direct, and it increases the force of a twitch but has no effect upon a tetanus. The exact mechanism of action remains unknown, but it does not seem to involve circulatory changes, release of potassium by the liver, or local alterations in ionic balance, and it is unaffected by cocaine or sympathicolytics. The above author believes it may normally play a helpful role in stressful situations. Finally, epinephrine under certain conditions will enhance conduction in peripheral nerves (see 39).

To what degree the preceding phenomena account for effects attributed to central actions of epinephrine or norepinephrine is difficult to assess. Many of them are best demonstrated by adding epinephrine to a perfusate which during the control period is epinephrine-free, an unphysiological situation, since both epinephrine and norepinephrine are normally present in blood, and are constantly being liberated at sympathetic nerve endings. Such effects may consequently be much less important in the intact preparation and resemble more the *permissive* effect of adrenal cortical hormones on certain processes which these hormones do not actually control. From a practical point of view, however, it is desirable to exclude these peripheral effects from the experimental situation whenever possible in order to simplify analysis and minimize error.

B. Cerebral vascular effects

Whenever any central action of epinephrine or a like substance is studied, the possibility that it acts indirectly by virtue of its effect upon cerebral blood vessels and blood flow always merits consideration. It seems desirable to evaluate these vascular effects before going on to presumably more direct actions. The effect of epinephrine upon cerebral vessels was the subject of a number of research efforts in the early 1900's. As might be anticipated, depending upon which report one reads, one can find evidence that epinephrine dilates cerebral blood vessels, constricts them, does both, one after the other, or does neither. No attempt will be made to review these earlier experiments, citations for which can be found in the more recent papers considered below.

In 1933, Forbes *et al.* (70) published one of a series of papers on cerebral circulation, in which they repeated and enlarged their earlier work on epinephrine, reviewed the literature and applied statistical techniques to resolve much apparently contradictory data. By observing cortical vessels directly through a window, they concluded that epinephrine applied locally to the cortex in a range of concentrations produced only vasoconstriction, that this constriction was feeble compared to the response of ear vessels, and that it seemed to affect only the larger and not the smaller arteries. Intravenous injections of 1 to 100 μg usually caused cerebral vasodilatation, more or less in proportion to the rise in blood pressure. Intracarotid injections produced vasodilation first, followed by vasoconstriction after the blood pressure had returned to normal.

Subsequently Fog (69) used a similar cortical window technique which allowed constant perfusion of the undisturbed cortex with Ringer's solution to which various concentrations of epinephrine and other drugs could be added. He found that epinephrine in concentrations of $1:10^4$ or $1:10^5$ constricted the arteries 3 to 30% (small by comparison to other arteries) but left the arterioles unaffected. He also studied the effect of intravenous injections of epinephrine, making use of a mechanical arrangement whereby the pressor response could be prevented or produced alone without epinephrine. He showed that cerebral vasodilation from intravenous epinephrine was entirely dependent upon the rise in mean pressure. If this was prevented, mild constriction, similar to that following topical application, was seen instead. He showed also that a rise in

pressure, however produced, caused a compensatory constriction of the arterioles, thus tending to maintain cerebral blood flow constant. Further studies (141), in which various sympathomimetic and parasympathomimetic substances were injected directly into the pial arteries, confirmed the finding that epinephrine constricts the larger but not the smaller pial arteries. More recently, Schmitt (236) has studied the effect of intravenous epinephrine and norepinephrine upon cerebral blood volume and thus blood vessels, using a type of cerebral plethysmography in dogs. Larger doses (50 μg) of both epinephrine and norepinephrine produced cerebral vasodilatation due to their pressor effect. Smaller doses (10 μg), which had little effect on blood pressure, produced vasoconstriction, epinephrine being more potent than norepinephrine. Curiously enough, if the blood pressure was lowered to shock levels (by bleeding, for example) then the effects of both epinephrine and norepinephrine were reversed, and they produced a cerebral vasodilatation which could be only partly accounted for by the rise in blood pressure.

Certain more indirect techniques have been applied to the same problem with less concordant results. Bouckaert and Jourdan (27) attempted to tie off all of the extracranial circulation in dogs and perfused the intracranial remainder at a constant stroke volume, interpreting increases in perfusion pressure as due to intracranial vasoconstriction. Epinephrine by intracarotid injection had this effect, as did stimulation of the cervical sympathetics. More recently, experiments in which great efforts were made to separate the extra- and intracranial circulation have again demonstrated decreased blood flow in the internal carotid artery, interpreted as vasoconstriction, in response to epinephrine; isoproterenol had the opposite effect (82). Using the venous outflow method, again with attempts to eliminate all the extracranial circulation, McClure and Green (143) were unable to demonstrate any reduction in cerebral blood flow from the intracarotid injection of 1 to 50 μg of epinephrine. With reference to negative results, in their recent review of the pharmacology of peripheral circulation, Bovet and Carpi (28) point out that an epinephrine-induced cerebral vasoconstriction which can be demonstrated in a lightly anesthetized animal in good condition will disappear with deep anesthesia (particularly barbiturates), respiratory acidosis, extensive surgery, shock, etc. They suggest that this loss of constrictor response may play a protective role in animals in poor condition where cerebral blood flow is already marginal.

Studies of cortical blood flow using thermoelectric flowmeters have shown that pressor doses of epinephrine increase cortical blood flow (115, 139). Using the nitrous oxide technique in man, King *et al.* (126) reported an increase in cerebral blood flow from epinephrine (22 to 73 μg per min intravenously), but a decrease from norepinephrine (9 to 28 μg per min intravenously), while the following year (1953) Sensenbach *et al.* (240), who administered the epinephrine and norepinephrine intramuscularly in oil in doses of 0.6 to 1.0 mg, found a decrease in cerebral blood flow from norepinephrine and no change from epinephrine.

Recently, Ingvar and Söderberg (112) have introduced a new method of re-

cording cerebral blood flow in cats by measuring with an interval counter the rate of venous outflow of the cannulated superior sagittal sinus after division of most of its extracerebral sources of blood. The method is very sensitive and capable of measuring brief and transient changes in flow, something for which many of the above techniques, especially the nitrous oxide one, are less suited. They found that intravenous epinephrine and norepinephrine (5 to 25 μg) both produced an increase in blood flow, apparently secondary to the pressor response, and that for equipressor doses of the two, norepinephrine produced less increase in flow than epinephrine, suggesting that it was exerting some vasoconstrictor action opposing the pressor effect. In a subsequent publication (111), intracarotid norepinephrine was shown to produce a brief vasoconstriction before the pressor effect had a chance to begin, followed by vasodilatation and increased flow once the blood pressure rose. Epinephrine on the other hand, showed no preliminary constriction but rather a slight dilatation, followed by further dilation once the pressor response became manifest. It was concluded that epinephrine may have a direct dilator effect on cerebral vessels.

The vascular actions of epinephrine and norepinephrine are further complicated by the fact that both compounds, as will be taken up subsequently, produce EEG activation. Ingvar (111) has shown that EEG activation, however produced, is associated with increased cortical blood flow, apparently a local reaction to increased demand by the nervous tissue, since it is largely independent of vasomotor reflexes. Furthermore, epinephrine, but apparently not norepinephrine, increases O_2 utilization of the brain generally (78, 126, 204).

There is no reason to assume, moreover, that all regions of the brain have the same vascular responses to agents such as epinephrine and norepinephrine. Actually local blood flow studies in the cat have shown that epinephrine has little or no effect on the blood vessels of the medulla but seems to produce a mild but rather prolonged vasoconstriction in the hypothalamus (234, 235). Further studies of this sort are needed.

In summary, it appears that both epinephrine and norepinephrine applied locally to the cortex of lightly anesthetized animals are purely vasoconstrictor, but rather feebly so, acting on the pial arteries but not the arterioles. Given intravenously in the same sort of preparation, their pressor effect generally overcomes the cerebral arterial vasoconstriction and produces passive dilatation, which is partly compensated for by arteriolar constriction tending to oppose changes in cerebral blood flow. Intracarotid injections produce a sequence of effects related to whether the systemic or local effects predominate. Deep anesthesia, extensive surgery, or deterioration of the preparation abolish or even reverse the responsiveness of the vessels. There is no agreement on the relative effectiveness of epinephrine and norepinephrine; studies on the anesthetized dog suggest that epinephrine is the more potent vasoconstrictor, while studies on man and on the unanesthetized cat indicate the reverse. In addition, both epinephrine and norepinephrine by virtue of their general effects upon cerebral metabolism and their specific capacity to produce EEG activation increase cerebral blood flow through local mechanisms. Finally, the effect of these two

agents on brain blood flow may vary from region to region so that overall studies can give a misleading impression of events in specific structures.

C. The blood-brain barrier

Epinephrine and norepinephrine are quite stable in blood and plasma; however, when injected into the circulation they are removed in a few minutes or less, principally by the liver, kidneys and the muscle masses of the trunk and extremities (119, 268). We have remarkably little direct evidence that they pass across the blood-brain barrier into the brain. Leimdorfer *et al.* (132) were unable to detect any epinephrine in the cerebrospinal fluid of cats after intravenous administration, despite the fact that epinephrine, as will be pointed out, is quite stable in this fluid. Raab and Gigee (203) found that intravenous infusions of epinephrine or norepinephrine had no effect on the concentrations of epinephrine-like substances in the brains of rats, while an infusion of DOPA produced a rise. Studies with C^{14}-labeled epinephrine in rats showed high counts in the liver, kidneys and plasma 3 to 4 hours after a subcutaneous injection, but the amounts in the brain were low and failed to show any trend over a period of time (233). Within 20 hours, all of the labeled epinephrine had been accounted for in the urine. This has been interpreted by some as indicating that epinephrine fails to pass the blood-brain barrier at all; such a conclusion is unjustified, however, since equally low and unchanging counts were found in the adrenals, ovaries, pancreas and spleen as well. A better interpretation is simply that the method reveals those locations where epinephrine is picked up and concentrated over a period of hours, and that the brain is not one of these, in the rat at least. Work currently in progress using tritium-labeled epinephrine suggests that there are regional differences in the blood-brain barrier to epinephrine, so that measurable amounts may enter the hypothalamus but not, for example, the cerebral cortex (8).

There is indirect evidence, however, that epinephrine does indeed penetrate the blood-brain barrier, since many experiments to be reviewed in the following section show that systemically administered epinephrine affects central nervous system function specifically, repeatably, and often within a single circulation time. It is the purpose of this section on Preliminary Considerations to take up all of the known ways in which epinephrine and norepinephrine affect central nervous system function *indirectly*; once these possibilities can be eliminated, however, it is a reasonable assumption that certain effects of epinephrine on the central nervous system are actually direct. Since very little is known about the intracerebral concentrations of epinephrine needed to achieve these effects, it is impossible at the moment to rule in or out a direct action on the basis of blood level or brain concentration alone. Certain central effects of epinephrine may well require only very small amounts.

There are a number of experiments, on the other hand, that clearly indicate that epinephrine instilled into the cerebrospinal fluid of the ventricles or subarachnoid space gets out into the systemic circulation very little if at all. Here it must be emphasized that the passage of substances from cerebrospinal fluid

to blood can be independent of their passage from blood to brain, so that knowledge of one barrier will not necessarily permit inferences about the other. Thus while several early papers claimed that the pressor response from intrathecal epinephrine was just as prompt and high as after intravenous injection, suggesting its rapid systemic absorption, in 1918 Auer and Meltzer (7) presented evidence emphasizing the differences in the pressor response in monkeys from epinephrine given intravenously versus injection by lumbar puncture. In an extensive series of studies on the hydrodynamics and pharmacology of the cerebrospinal fluid, Becht (15) showed that intracisternal epinephrine in cats produced no pressor response at all—rather a slight fall or no change, provided that a bloody tap was scrupulously avoided; furthermore, epinephrine could be recovered from the cistern up to 6 hours after injection, attesting to its stability in cerebrospinal fluid. These findings were repeated by Heller (90) who showed that lumbar puncture in cats and dogs (unlike primates and man) almost always injures the spinal cord, with leakage of the injected material into the circulation. If done by laminectomy and under direct vision, however, the results were the same as for intracisternal injection of epinephrine, *i.e.*, no blood pressure effect in dogs and generally some fall in blood pressure in cats. The lack of a pressor response has subsequently been confirmed after intraventricular injection of epinephrine in dogs (255) and after intracisternal (132, 133) and intraspinal injection in man (201).

In summary, epinephrine remains stable in blood and is selectively removed from the circulation by certain organs, but not the brain. Its precise capacity to cross the blood-brain barrier is unknown but probably small, and it may show regional variations. Indirect evidence suggests that it can penetrate sufficiently to exert some central effects, however. There is no evidence, on the other hand, that it can be transported intact into the general circulation from the cerebrospinal fluid, where it remains for hours.

D. Reflex effects; possible direct effect upon the vasomotor center

While the significance of central effects of epinephrine and norepinephrine mediated by changes in cerebral blood flow or the peripheral nervous system remains problematical, there is one important and generally recognized indirect mechanism by which these compounds modify brain activity, *viz.*, that working by means of the carotid and aortic baroreceptors. Since the investigation of this effect has gone hand in hand with study of possible direct depressant effects of epinephrine and norepinephrine upon the vasomotor center, they will be considered together.

Early in the investigation of the circulatory effects of epinephrine, the possibility that all its effects were centrally produced was seriously considered. Further study showed all the pressor effects and at least some of the subsequently discovered depressor effects to be mediated peripherally, but the possibility remained that at least some of the vasodilatation was centrally induced, either directly or reflexly. With the elucidation of the peripheral baroreceptor and chemoreceptor mechanism by Heymans and his collaborators in 1933 (95),

it became apparent that any influence tending to raise the blood pressure stimulated the pressure-sensitive elements in the carotid sinus and aortic arch, which then in turn fired impulses into the vasomotor center tending to inhibit its activity and restore the blood pressure back down to normal. Epinephrine was no exception, and insofar as it raised the blood pressure, it induced reflex vasodilatation and cardiac slowing. It was subsequently shown (19, 50, 96, 97, 148) that epinephrine and norepinephrine perfused through or applied locally to the carotid sinus induce contraction of the smooth muscle there. This stimulates the receptors directly (causing a drop in blood pressure) and sensitizes them to intracarotid pressure rises so as to exaggerate their reflex responses. Such an effect can be prevented by adrenergic blocking agents and may play a normal role, through adrenergic nerves in the sinus wall, in setting or adjusting the responsiveness of this receptor mechanism. It seems then that epinephrine and norepinephrine stimulate the baroreceptors both through the induced rise in blood pressure and directly as well, all tending to depress the vasomotor center (see review by Heymans (94)).

Recently Bonvallet *et al.* (22, 55) have demonstrated that this depression is not confined to the vasomotor center but extends to the reticular activating system as a whole, the depression tending to deactivate the EEG and lessen the tonic facilitatory influence of this system upon spinal motor mechanisms. The opposite effect, EEG activation and increased spinal facilitation, results from a fall in blood pressure or any other event which decreases the tonic inhibitory bombardment of the brain stem by the baroreceptor elements of the vagus and glossopharyngeal nerves.

Returning to the possibility of a direct inhibition of the vasomotor center by epinephrine, work published in several laboratories on dogs in 1927 revived this possibility by demonstrating vasodilatation in neurally intact but vascularly isolated organs (kidney, hind limb) upon administering epinephrine to the general circulation. In at least one case, the vasodilatation seemed independent of the rise in blood pressure, occurring without it (72, 257). The following year, 1928, Heymans (93) published experiments in which the head circulation of a test dog was separately perfused by a donor animal. While injection of epinephrine into the head circulation caused a fall in blood pressure of the body, the effect was completely abolished by cutting the four moderator nerves and the author concluded that the depressor response was purely reflex in origin and not central. Tournade (259) next summarized the dispute and presented new data on the separately perfused but neurally intact dog's paw showing that the paw underwent vasodilatation from administration of epinephrine into the general circulation even after all four moderator nerves were cut, again suggesting a direct central effect. In the ensuing discussion (fortunately transcribed) Heymans suggested that Tournade's results could be explained by the presence of additional undenervated baroreceptors, or through changes in blood CO_2 or O_2 tension brought about indirectly by the effects of epinephrine on respiration, metabolism, etc. The same year, Tournade and Malméjac (258) endeavored to answer each of these criticisms by presenting new data in which the test animal

had the head circulation perfused by one donor animal and the paw circulation perfused by a second donor. Again epinephrine injected into the head circulation of this dog produced vasodilatation of the paw. Respiratory effects were eliminated because the donor animal supplying the head circulation was on artificial respiration, and stimulation of additional baroreceptors in the test animal's body was excluded since the epinephrine reached only the head and did not affect the systemic blood pressure.

Using a slightly different technique, Nowak and Samaan (189) showed vasodilatation in the limbs after adding epinephrine to the separately perfused head circulation. After section of the moderator nerves, the effect persisted but was much diminished. It could be duplicated by raising artificially the head perfusion pressure, suggesting that there were additional pressure-sensitive elements in the head or neck still undenervated, or that an increase in the perfusion rate had some nonspecific effect upon brain excitability. They concluded that epinephrine had no specific central vasodepressor effect.

More recently, in an impressive series of experiments, Taylor and Page (255) described a technique in which they went to great pains to separate the body circulation of experimental dogs from the head, which was then separately perfused. Injection of 10 μg of epinephrine or norepinephrine into the head circulation resulted in a fall in blood pressure of the body which was diminished but far from eliminated by section of the moderator nerves. Mechanically induced changes in blood pressure, mimicking those of epinephrine, had much less effect than epinephrine itself. The depressor response depended upon spinal cord tracts descending in the anterolateral quadrants, as well as the sympathetic nervous system. They concluded that there are chemoreceptors within the brain which respond to epinephrine and norepinephrine by inducing a fall in blood pressure through inhibition of sympathetic tone and perhaps even an active vasodilatation via sympathetic pathways.

Unfortunately, after 30 years of research, the matter is still not settled. Schneider *et al.* (237) have recently reported attempts to repeat the experiments of Taylor and Page, using what they believe to be an improved and less traumatic way of separating the head and body circulations. They found that over half of the depressor response from injecting epinephrine into the cranial perfusion was due to increase of perfusion pressure from epinephrine and could be eliminated by using a perfusion pump; of the rest, most of it was eliminated by section of the moderator nerves and was apparently due to the direct effect of epinephrine and norepinephrine upon the receptors previously described. All that was left was a very small and inconstant depressor response, possibly due, by exclusion, to a central depressor effect. They then calculated that the epinephrine blood level required to elicit this effect was 10 to 100 times the concentration which might be reached under most circumstances and was therefore unphysiological.

It should be emphasized that with the exception of the experiments of Bonvallet *et al.* (22), *all* the other experiments mentioned above were done under anesthesia, and as will be discussed later anesthesia tends to abolish certain

central effects of epinephrine and norepinephrine or even to reverse them. Thus none of the data for or against central depression of the vasomotor center by epinephrine is necessarily applicable to the intact, unanesthetized animal. Using venous plethysmography in awake human subjects, some sympathectomized, Swan (252) demonstrated vasodilatation of the hand following an intravenous infusion of epinephrine. This did not occur in sympathectomized limbs nor if the epinephrine was given intraarterially instead. He concluded that the vasodilatation was a direct result of the epinephrine infusion and was mediated by the sympathetic nervous system. However, there is no way here of distinguishing a direct central effect from one reflexly induced, and a depressant action upon sympathetic ganglionic transmission (*q.v.*) is an equally good explanation. Certain unpublished observations of the writer in which the central effects of intravenous epinephrine and norepinephrine were progressively modified by chlorpromazine in the unanesthetized, curarized cat strongly suggest that under these particular circumstances epinephrine and norepinephrine may stimulate the vasomotor center and raise the blood pressure, quite independently of their peripheral effects, which are suppressed or reversed by the chlorpromazine. Furthermore, it was possible to obtain an elevation of blood pressure from microinjections of epinephrine into certain regions of the brain stem.

In summary, epinephrine and norepinephrine increase the activity of the carotid and aortic baroreceptors both by direct stimulation and sensitization, and by raising the blood pressure. This results primarily in increased inhibition of the vasomotor center, but it also inhibits other brain stem mechanisms including the respiratory center and the ascending and descending reticular activating systems. Since all of the blood pressure lowering effects of the catecholamines cannot be accounted for by the above action alone, a direct inhibition of the vasomotor center through intracerebral chemoreceptors has been postulated. It remains to be shown, however, that this latter mechanism plays any role in the intact, unanesthetized organism and in the presence of physiological blood levels of epinephrine or norepinephrine.

III. CENTRAL EFFECTS

A. Spinal cord

Some of the earliest observations on the pharmacology of spinal cord responses were made by Johnson and Luckhardt (188) when they reported on the effects of ephedrine in dogs anesthetized with barbital. Since it is likely that the central actions of ephedrine are closely related to those of epinephrine, references will be made to this and related compounds wherever it appears helpful. These authors found that ephedrine increased the knee jerk in their animals, and that this effect persisted after thoracic cord section. Since the neurological change did not correspond in time to the elevation in blood pressure, they concluded that the drug acted directly on the cord. These results were subsequently confirmed in decapitate dogs (101) and also in the spinal monkey (114), in which the additional interesting observation was made that after hemisection of the spinal cord, the reflexes were enhanced only on the denervated side. These last authors also

gave epinephrine subcutaneously, three doses every ten minutes, and obtained effects which were similar to ephedrine but less pronounced and much shorter in duration.

In 1937, Schweitzer and Wright (239) undertook a systematic study of the effects of epinephrine on the knee jerk (a monosynaptic extensor reflex) in the cat under chloralose. Doses of 200 to 400 μg produced long-lasting diminution or abolition of the knee jerk, sometimes preceded by preliminary facilitation. They carefully eliminated neuromuscular block and action via the baroreceptors as possible sources of this effect, and were still able to obtain it after thoracic cord section. It was easily dissociated from the pressor response and was unaffected by cocaine, eserine or thyroid hormone. They concluded that epinephrine probably acted directly upon the cord, but admitted that the doses necessary to obtain the effect were unphysiologically high. Using an indirect index of spinal cord reflex excitability, Bonvallet and Minz (24) found that in the spinal cat epinephrine produced a decrease in excitability which could be blocked by both ergotamine and atropine; in the thalamic animal, however, epinephrine produced an increase in excitability, blockable by ergotamine but not by atropine. They concluded that the direct depressant action of epinephrine upon the cord somehow involved a cholinergic link, but that its excitatory effect on cord mechanisms mediated through the brain stem seemed specific and independent of cholinergic pathways.

Studies by Bülbring and Burn (35) showed that in the case of the separately perfused cord and leg, the addition of small amounts of epinephrine increased and stabilized the muscular response to an injection of acetylcholine into the cord perfusate. Given alone, small doses had no effect upon the knee jerk but larger doses (100 μg or more) produced augmentation; ephedrine and amphetamine had a similar effect but eserine depressed the knee jerk. In his review, Burn (39) summarized this and other evidence showing that in many situations where epinephrine had little or no effect itself, it profoundly modified the response to acetylcholine, small doses usually producing facilitation, larger doses the reverse. In a subsequent paper, Bülbring, Burn and Skoglund (38) reported the results of epinephrine and acetylcholine in a preparation in which spinal movements were induced by stimulation of the medulla. All possible effects—facilitation, inhibition, etc.—were obtained from each agent, depending on the particular circumstances. The only generalizations permissible seemed to be that at any one time the effects of epinephrine are opposite upon extensors and flexors, and always opposite to those of acetylcholine. The cats used in these experiments were decerebrate, unanesthetized, and had most of the dorsal roots sectioned; however, the fact that the stimuli were applied to an intact lower brain stem makes it impossible to exclude effects of epinephrine at suprasegmental levels.

Stavraky (59, 251), in studies of central denervation hypersensitivity, has been able to show the exaggeration of the response to epinephrine or the appearance of one previously unobtainable by performing certain denervation procedures. Cutting the dorsal roots unilaterally will, after about 18 hours, result in a progressive increase in the motor response of the quadriceps (a physiologic extensor) to an intraarterial injection of epinephrine directed to the cord; chronic

nephrine seems to be important in facilitating the actions of acetylcholine, whereas excessive doses have the opposite effect on it. On the other hand, epinephrine itself seems to have a definite facilitating effect upon certain reflex mechanisms, in particular the extensor reflexes, although again very large doses may have the opposite or a polyphasic effect. In all the experiments cited above it was necessary to use doses considerably above the physiologic range to obtain any effect at all, and this should always be kept in mind. It does not necessarily mean that all the above results have only pharmacologic significance, however. If, as Bernhard and Skoglund (17) suggested, epinephrine should be a normal transmitter at some of these synapses, blood levels tell us very little about the necessary local concentrations.

B. General behavioral and neurologic effects

1. Epinephrine arousal. Epinephrine seems to be popularly associated with excitement or nervousness, and patients who have received a subcutaneous injection for one reason or another will attest to this. After 0.5 to 1.5 mg intramuscularly or subcutaneously in man, certain somatic signs and symptoms predominate and may obscure the "central" effects. A muscular tremor, involving the hands and often the lower extremities, trunk, lips and voice as well, is almost invariably noted. The next most common finding is a consciousness of increased heart action which may be prominent enough so that the subject can count his pulse by it. Other less often reported effects include hyperpnea, salivation, tearing, urinary urgency, cold or tingling extremities, substernal oppression, headache, etc. (13, 41, 61, 77, 117, 150). There are in addition a variety of more purely subjective reactions to epinephrine including excitement, tenseness, exhilaration, and restlessness, or anxiety, agitation and fear. Even hallucinations have been reported (104). In an attempt to explore the nature of these "emotions" produced by epinephrine, certain investigators (41, 150) have made a distinction between a "true" emotion, and a "cold" emotion in which the experience is not genuine, makes the patient feel "as if," or simply reminds him of the way he felt when experiencing a true emotion in the past. In most subjects the "emotions" produced by epinephrine were of the "cold" variety. Although in the few subjects experiencing "true" emotion it was always one of fear or anguish, those experiencing a "cold" emotion were about equally divided between pleasant and unpleasant reactions, and many felt neither. The tendency to react emotionally is much greater in excited or hyperthyroid individuals (150), and in those who are normally emotionally labile, in which case the symptom pattern tends to resemble the subject's previous pattern of anxiety (13). On the other hand, the administration of norepinephrine seems to be remarkably symptom-free, even with substantial elevations in blood pressure (77, 126), or to produce mild and "unfamiliar" symptoms (253).

It may of course be argued that most critical subjects will not report a "true" emotion such as fear in the absence of a reasonable cause, no matter what they feel. On the other hand, since so many subjects feel no emotion, or feel something lacking authenticity, sometimes pleasant, sometimes unpleasant but often

hemisection of the spinal cord has the same effect. The excitatory effects were shown to be very sensitive to anesthetics.

Bernhard and co-workers (16, 17, 18) have published an interesting series of papers in which they were able to demonstrate a rather selective effect of epinephrine upon extensor and flexor reflex mechanisms. Thus epinephrine applied locally to the cord (1:10,000) increased the negativity of the ventral root steady potential, a change already shown to be accompanied by extensor facilitation, and at the same time there was a demonstrable increase in extensor activity. In a study of reflexes in the spinal cat with many of the dorsal roots cut in addition, 100 to 200 μg of epinephrine given intravenously enhanced the monosynaptic extensor reflex but left the monosynaptic flexor reflex depressed or unaffected. Intraarterial doses of 10 to 15 μg were also effective. Acetylcholine generally had the opposite effect. These workers concluded with the interesting suggestion that epinephrine be investigated as a possible transmitter substance in the central nervous system.

In studying the effects of epinephrine upon reflex and cortically induced movement, Sigg *et al.* (246) found that reflex facilitation disappeared after destruction of the hypothalamus or after deepening the anesthesia, to be replaced by an inhibition which persisted even in the spinal animal (see III, F). Working with spinal or decerebrate cats, Wilson (272) observed facilitation of the crossed extensor reflex from 5 to 10 μg of epinephrine injected intraarterially to the cord; larger doses had the same effect but with the addition of a preceding and a succeeding depressor phase. The effect on polysynaptic reflexes tended to be variable, often enhancement. The results in the spinal cats were much clearer than in the decerebrate cats and the author concluded that exclusion of descending brain stem influences was very important in studying purely spinal effects. Currently Eccles and co-workers (53) have extended their pharmacologic studies of the spinal cord, in particular of the cholinoceptive Renshaw cell. Their preparations were anesthetized with pentobarbital and great pains were taken to exclude extraneous influences by performing low cord section, dorsal root deafferentation, and close arterial injection. Surprisingly enough, they obtained very little effect from epinephrine, norepinephrine or ephedrine (5 to 100 μg)—usually only a late and long-lasting facilitation which they felt could be due to vasoconstriction and consequent anoxia.

It is difficult to derive an orderly picture from the preceding data, but certain features are apparent. In studying the direct effects of epinephrine and norepinephrine at the spinal level, it is essential to eliminate descending suprasegmental influences, which otherwise dominate or confuse the picture. The additional features of close arterial injection and dorsal root section further restrict the site of action to the cord itself and are probably desirable, although this has not been proved. Moreover, where the central effects of epinephrine are concerned, no experiments can be considered definitive or complete if carried out only in anesthetized preparations. Once these sources of confusion are eliminated it still appears that the catecholamines have several, probably distinct and mutually interfering effects upon cord function. A certain basal level of epi-

neither, it seems more plausible that the few reports of "true" emotion were either due to powerful conditioning of the subject by past experiences accompanied by the same somatic sensations, or that true fear was produced directly by the doctor, the injections, or the disturbing somatic sensations, and not the epinephrine *per se*. It is likely that epinephrine has some central action in the above situations, probably more of an unspecific arousing or exciting nature, accounting for the common complaints of tremor, restlessness, and anticipation, and that any "emotion" produced is a result of this nonspecific arousal superimposed upon the subject's reaction to the experimental situation itself or the particular associations the somatic sensations may have for him. Some experimental support for this comes from the observations of Sharpless (242) on the effects of epinephrine and norepinephrine on conditioned avoidance in the rat. Intravenous injections of 1 to 5 μg/kg had no effect upon the animals' preference in a T-maze, whereas mild electric shock or intravenous histamine were very effective.

Although norepinephrine is said to lack these central excitatory effects, it should be pointed out that most of the preceding observations upon epinephrine were made after subcutaneous or intramuscular injections of fairly large doses, with the effects prominent and long-lasting. Administration of norepinephrine in similar dosage and route may be dangerous, so that studies upon it are limited to a few observations, usually during intravenous administration, when the dose was sharply limited by the pressor response.

We have made observations on epinephrine arousal in unanesthetized cats (219). Animals were prepared with permanently implanted cortical electrodes and a venous catheter, making it possible to inject epinephrine intravenously into the undisturbed animal and at the same time observe its behavior and record the EEG. Doses as small as 2 to 5 μg/kg produced repeatable EEG activation and behavioral arousal in the naturally sleeping cat. This threshold remained quite stable for hours and could be measured fairly accurately, provided care was taken to avoid temporal conditioning by injecting the epinephrine at varying time intervals, and provided at least 3 minutes elapsed between injections. In case of shorter intervals there was a rise in threshold due to an apparent inhibitory effect of epinephrine upon EEG activation mechanisms which followed the activation period and which had not been given time to wear off.

2. Epinephrine stupor. By contrast, larger doses of epinephrine seem to have quite the opposite effect. As mentioned in the Introduction, observations on these striking behavioral effects of epinephrine began very early in the history of experimental medicine, the first experiments having been prompted by interest in cocaine anesthesia and the possible benefits to be derived from adding epinephrine. Thus Dönitz (57) in 1903 reported giving 1 mg of epinephrine to three cats by lumbar puncture; one animal vomited, another collapsed and the third was unaffected. He was sufficiently emboldened by these results to add it to the spinal cocaine anesthesia then being used clinically and reported that it improved the anesthesia and reduced the toxicity of cocaine. The following year, Zeigan (275) disputed these latter findings, claiming that Dönitz overestimated the

toxicity of cocaine to begin with. He himself undertook a similar series of experiments, administering 1 mg of epinephrine by lumbar puncture to cats, and reported the appearance of anesthesia of the lower half of the body, lasting some 8 to 12 minutes, and followed by seizures of the lower extremities if repeated. Of much greater interest is his observation that if the same dose was given in 5 ml of saline and the animal's head lowered there occurred the fairly rapid onset of deep sleep and total analgesia with retention of reflexes. By injecting methylene blue the same way, he observed its rapid diffusion to the basilar cisterns and even over the hemispheres, and he concluded that the unconscious state was due to vasoconstriction and consequent anemia of the brain.

The same year Weber (269) independently reported similar results, having found that 1 mg of epinephrine by lumbar puncture produced insensibility to pain distal to the injection site but that it was ineffective in producing a peripheral nerve block. He also injected epinephrine directly into the carotid artery; the dosage and details of the technique were not included in the paper, since apparently its presentation was immediately followed by a practical demonstration to his audience. He described the prompt appearance of salivation, followed in a few moments by the onset of sleepiness and analgesia. While the cat did not object to such stimuli as cutting the ears, piercing the nasal cartilage, or burning the tail, it nonetheless blinked to light, sneezed from ammonia, and flinched from a sudden handclap. Because of this rather selective depression of pain appreciation and consciousness, he reasoned that epinephrine must exert some rather specific action on the actual "organs" of pain perception, presumably centrally, since he could not demonstrate peripheral effects. Subsequently Biberfeld (20) reinvestigated the lethal dose of epinephrine by lumbar puncture and found it to be 5 mg for the average cat. He observed paralysis of the lower extremities, and a paralytic dilatation of the pupils in addition. Of particular historical interest were his trials of norepinephrine; he found it as effective as epinephrine but less toxic, and recommended that it be used more generally. Bass (14) likewise observed deep sleep and profound analgesia in dogs after the injection of 6 to 8 mg of epinephrine subdurally or even intracerebrally. He recorded a fall in body temperature and remarked on the conspicuous retention of corneal, pupillary and tendon reflexes. In considering all this early work, it is probably advisable to discount the reports of distal or segmental anesthesia or analgesia from epinephrine administered by lumbar puncture because, as was previously pointed out, such injections so frequently injure the cord. However, 0.2 to 1.0 mg of epinephrine given alone as a spinal anesthetic to women in labor did produce definite but variable effects ranging from a complete saddle block to barely detectable analgesia without further neurologic involvement. The investigators doubted that it acted by vasoconstriction but were hesitant to use larger doses to try and obtain more consistent and useful results (201). The general alterations in pain perception and consciousness deserve attention, however, and have been confirmed in a variety of subsequent experiments.

Interest in epinephrine analgesia revived again after the detailed report of Ivy *et al.* (113) in which they described the results of administering epinephrine

(100 μg/kg) to unanesthetized dogs either intravenously or into one carotid artery. They observed some rather variable early effects including excitement, stupor, vomiting, opisthotonus, spasticity and even "mild convulsions." Then all the animals showed a period of analgesia of 60 to 90 minutes, profound enough to permit abdominal laparotomy in some instances. Throughout this period, consciousness was apparently retained, there was no ataxia, and the animals were observed to sneeze, scratch, and chase fleas. Quantitative measurements of pain threshold by the tooth pulp method showed it to be markedly elevated 60 minutes after the injection. There was no evidence presented to suggest that the intraarterial route was any more effective than the intravenous one. Much smaller doses of epinephrine, given subcutaneously to human subjects produced a modest elevation in pain threshold in some.

Leimdorfer *et al.* (132) directed attention to alterations in blood sugar following intracisternal epinephrine, a subject which will be taken up subsequently. They noted that with doses of 0.5 to 1 mg of epinephrine their unanesthetized cats showed momentary excitement and a widened gait, then became drowsy for up to 18 hours; they also administered 2 mg of epinephrine intracisternally to a nonnarcotized patient, who showed drowsiness and sleep one hour after the injection. In dogs, 0.5 to 1 mg/kg intracisternally produced initial excitement followed in 10 to 15 minutes by sedation and in 30 minutes by sleep lasting several hours, deep enough for surgical laparotomy. There were no ill effects upon recovery unless the dose exceeded 2.5 mg/kg and there were no changes in blood pressure, EKG or EEG at any stage (133). Subsequently, Leimdorfer (131) compared a variety of sympathomimetic amines for their intracisternal effects. Epinephrine, norepinephrine, isopropylarterenol and butanephrine all produced stupor or sleep, as did synephrine and paredrine to a lesser extent. Neo-Synephrine, ephedrine, amphetamine (Benzedrine), propadrine and tuamine all produced great excitement, however. The author related the sedative effect to the catechol moiety, but felt that the excitement was related to the structure of the aliphatic chain.

Injections of 20 to 80 μg of epinephrine or norepinephrine into the lateral ventricle of the unanesthetized cat produced a state described as resembling light pentobarbital anesthesia, often preceded by swallowing, retching or vomiting (67). Instillation of 5 to 250 μg into the lateral ventricle of psychotic human subjects produced a lowering of muscular tone and flushing, followed by drowsiness and light sleep (244). Injections of 1 μg of epinephrine directly into the brains of mice (much of it reaching the ventricular system) produced increase in respiration, excitement and exophthalmos, followed in 15 minutes or so by a state of deep sedation (87) lasting 5 to 8 hours.

We have repeated the intraventricular administration of epinephrine to cats, using the method of Feldberg and Sherwood, and monitored the EEG through implanted electrodes at the same time. Shortly after the injection, the latency varying inversely with the dose, the cat retches or vomits several times; with large doses (2 mg) this may come on within one minute; aside from the natural disturbance accompanying this, there is no noticeable excitement. Respiration

however, is stimulated and becomes progressively more so. We have measured a a respiratory rate of over 200/min, sustained for several hours. Gradually the cat becomes inactive, sitting blankly for periods and showing none of the usual exploratory or affectionate behavior. Finally, within 10 to 20 minutes, it lies down in a sort of stupor which gradually becomes deeper for perhaps 45 minutes or an hour, then clears gradually. At the height of the effect, the animal shows no spontaneous behavior, lying with eyes open, immobile except for the panting. There is never any wild or incoordinate behavior so characteristic of slow barbiturate induction. Segmental reflexes (extensor stretch reflexes, limb withdrawal, corneal, conjunctival, pinna and vibrissae reflexes) are brisk and active as are sneezing, coughing and swallowing. The animal appears extremely weak and cannot support its weight or right itself. Yet it may respond by an exaggerated flinch to loud sound or sudden touch, and the rapid and deep respiration attest to the absence of any neuromuscular or spinal block. There is also a conspicuous analgesia, or at least the conspicuous absence of any generalized behavioral response to painful stimuli. It is possible to pinch the toe pads, lips, tongue, ears and tail very severely, or to rest one's finger on the cornea and, provided it is done gradually so as not to invoke a segmental withdrawal reflex, the cat will tolerate it without objection. Although the analgesia is quite impressive, it is doubtful if it is complete enough in the cat to permit laparotomy such as has been performed in dogs in this state. The analgesia and stupor seem to appear hand in hand; we have never observed analgesia in a completely alert animal (219).

While there are no specific or pathologic EEG changes accompanying all this, certain features are impressive. During the induction period, it is customary to see bursts or varying periods of slow activity characteristic of drowsiness, with occasional spindles, and a certain amount of similar activity is seen during recovery. During the height of the stupor there may still be some activity characteristic of the lightly drowsy cat. More impressive, however, is the fact that these periods alternate with long, very conspicuous periods of marked EEG activation, characteristic of the alerted cat, even though the animal is lying prostrate and *apparently* unconscious. This may represent another example of EEG-behavioral dissociation, of which the best known instance is the atropinized animal in which the EEG is characteristic of sleep even though the animal is walking about, excited. Another interesting EEG feature is the appearance of exaggerated photic driving with irradiation of the cortical response to frontal regions (219).

A very similar neurologic syndrome is described by de Jong (120) in cats receiving 20 mg of epinephrine subcutaneously. He emphasized the vegetative effects (including the vomiting, salivation, and polypnea), and the marked decrease in motor initiative going on to catalepsy, and called the complete syndrome "catatonia." Of particular interest is his observation that other drugs (including bulbocapnine, mescaline, and large doses of acetylcholine) as well as physical insults to the nervous system (electroshock, anoxia) were also capable of reproducing most or all of the catatonic syndrome. He concluded that it constitutes a general reaction-pattern of the nervous system, like seizures or coma, and

is quite unspecific. A comparable picture is seen if epinephrine is infused intravenously in the waking cat (241). In doses of 2 μg/kg per min, epinephrine produced depression of a conditioned response; in larger doses (4 to 6 μg/kg per min), stupor occurred, often preceded by vomiting, the latency of onset being inversely related to the dose.

In cats with permanently implanted carotid catheters and cortical electrodes (216), injections of 1 to 250 μg of epinephrine into the carotid circulation are without lateralizing neurological effects except for dilatation of the ipsilateral pupil—in contrast to barbiturates, eserine, chlorpromazine, curare, or procaine, all of which produce either excitatory or paralytic phenomena clearly lateralized, at least within the first circulation time, to the opposite side of the head and body. After a few minutes, there is retching, then mild sedation, wearing off in 15 to 20 minutes (218).

3. Epinephrine analgesia. Reference was made in the preceding section to the rather conspicuous analgesia that accompanies epinephrine stupor. In Ivy's experiments on dogs (113), the analgesia was apparently much more conspicuous than the stupor, and some analgesia could be demonstrated in human subjects without stupor at all. The reader is referred to this paper for an interesting review of attempts to use epinephrine and its congeners as analgesic agents therapeutically. Some efforts seem to have met with success, especially in the treatment of the chronic pain of leprosy. Gross *et al.* (85) describe an elevation of pain threshold from 0.2 to 1.0 mg of epinephrine subcutaneously in man, followed by a period of hypersensitivity to pain afterward. Needless to say, pain is an intensely subjective experience and quite difficult to measure, and it is not surprising that many of these results have not been confirmed or that other investigators have found the opposite. Thus Wolff *et al.* (274) found that 1 mg of epinephrine decreased or abolished the analgesic effect of 10 to 15 mg of morphine, and Milošević (168) has made comparable observations in mice, in which he observed that epinephrine (0.5 mg/kg) had no analgesic effect of its own, although it did produce some sedation, and that combined with morphine, methadon or pethidine, epinephrine antagonized their analgesic effect. On the other hand, the same dose of epinephrine did have a prolonging effect on intravenous anesthesia from barbiturates, paraldehyde, chloralose and ethanol (169). Likewise, attempts to show any analeptic activity of epinephrine or norepinephrine have been unsuccessful (254). An analgesic effect has been claimed for ephedrine, amphetamine and several related sympathomimetic agents (125).

4. Psychological effects. This category is unavoidably vague as the rapid progress of experimental and physiological psychology has blurred the distinction between behavioral and neurophysiological events. Hoagland in 1928 (102) studied the immobilization phenomenon in the lizard Anolis, an animal which will remain quiet for a certain period if suddenly turned onto its back. While injections of adrenaline would not provoke this immobility, they did prolong the interval between recoveries, and the author naturally speculated whether epinephrine normally played a contributory role in this specialized form of behavior, or even in the behavior commonly observed in a variety of animals referred to as being

"paralyzed with fear," etc. In specific psychological test situations, epinephrine has been reported to improve maze learning (3), and to increase the intensity of conditioned reflexes in small doses but to decrease it with large ones (200). It impaired certain conditioned reflexes in the experiments of Gantt and Freile (71), and produced a marked decrease in conditioned avoidance in rats in doses which also made the rats lethargic and generally depressed (128). The intravenous infusion of as little as 2 μg/kg per min clearly depressed a hunger-motivated conditioned response in the cat (241), whereas single intravenous injections of 1 to 5 μg/kg in the rat failed to influence its choice in a T-maze (242). Given subcutaneously to normal subjects, 0.5 to 1 mg of epinephrine slightly diminished capacity for mental arithmetic, left free association unimpaired, and actually improved strength and motor tapping rate (117). Intravenously in very small doses (5 μg/kg per hr) it impaired performance in some motor tests, but left perception unaffected (13).

More recently, Olds and Olds (192) have demonstrated a positive reinforcement from injections of epinephrine (1.4 μg in 1/700 ml) into the hypothalamus of rats. The injections seemed to produce muscular incoordination and the self-injection rates were rather slow and equivocal. The response to iproniazid, which may act through adrenergic mechanisms, was clearly positive, however, while acetylcholine and serotonin had no such effect.

In summary, epinephrine in man produces a variety of subjective complaints like restlessness and anxiety, whereas norepinephrine apparently does not. A single comparatively small intravenous injection of epinephrine will regularly and consistently wake the naturally sleeping cat. Larger doses of epinephrine or norepinephrine, on the other hand, given into the carotid artery, by intravenous infusion, subcutaneously, or intrathecally by ventricular, cisternal or lumbar puncture produce a characteristic syndrome of stupor, coming on gradually with a long (10 to 15 minutes) latency and lasting many minutes or hours. This is generally preceded by vomiting, retching and respiratory stimulation, and depending on the species, varying degrees of excitement. The stupor itself is not comparable to natural sleep or barbiturate anesthesia; the eyes remain open, segmental and bulbar reflexes are active or overactive, but the behavioral response to pain is diminished or absent. Analgesia without stupor has been reported in dog and man, but is not seen in the cat, rat, or mouse. Moreover, epinephrine seems actually to antagonize the analgesic effect of narcotics. Small doses can improve some conditioned reflexes, but larger doses, particularly those producing stupor, impair them. Epinephrine may have a positive reinforcing ("rewarding") effect when injected directly into the hypothalamus of rats.

C. Neuroendocrine mechanisms and the hypothalamus

1. Vasopressin release. In 1945, O'Connor and Verney (190) observed that the antidiuresis caused by vasopressin in response to emotional stress was greater and more consistent in sympathectomized dogs, and that an injection of epinephrine before the stress could inhibit the antidiuretic response. It has since been shown

that epinephrine can block a whole sequence of events occurring in the dog from burns or operative stress, including an increase in serum antidiuretic hormone, its fall in the neurohypophysis, loss of neurosecretory material from the supraoptic and paraventricular neurones and neurohypophysis, and an increase in acetylcholine concentration in the neurohypophysis (245). Experiments by Duke and Pickford (60) showed that epinephrine inhibits the antidiuresis produced by an intracarotid injection of acetylcholine. More detailed studies of this phenomenon (1) revealed that 0.5 to 3.0 μg of epinephrine regularly block the antidiuretic response from 200 μg of acetylcholine, provided that it is given 8 to 45 minutes beforehand; curiously enough, larger doses of epinephrine are progressively less effective. Because of this latter finding, they felt that inhibition through vasoconstriction or even direct inhibition of the supraoptic neurones was unlikely, but postulated the stimulation by epinephrine of inhibitory neurones projecting to the supraoptic nucleus; smaller doses of epinephrine were felt capable of exciting this inhibitory pathway, whereas excessive doses progressively paralyzed it. The writer finds this explanation altogether reasonable, but it is only fair to add that in view of the complex and bivalent effects of epinephrine upon cholinergic transmission (39) the results might still be due to a direct influence of epinephrine upon the presumably cholinoceptive supraoptic neurones, but one which shows a relationship to concentration the opposite of that manifested by peripheral systems so far studied. Actually, when one makes inferences from end-results about the composition of central inhibitory and excitatory neuron chains, a number of algebraic solutions is naturally possible.

Another instance of hypothalamic inhibition by epinephrine has been reported by von Euler and Holmgren (267), who found that they could inhibit the activity of the thyroid gland (as measured by its release of radio-iodine) by minute injections of epinephrine (2 μg in 2 μl) directly into the mamillary bodies. Similar injections into the anterior pituitary gland itself were without effect. Injections of thyroid hormone, on the other hand, inhibited thyroid activity if injected into the pituitary but not after injection into the hypothalamus.

2. ACTH and the adrenal cortex. Early in this decade, when interest in the adrenal cortex and its control mechanisms had reached a new high, one of the most stimulating hypotheses concerning the release of pituitary ACTH and consequently of adrenal 11-oxysteroids in response to stress was that which implicated epinephrine as the common denominator. While a direct effect of epinephrine upon the pituitary remained a distinct possibility (144), its action upon the hypothalamic centers concerned with pituitary ACTH regulation was suggested as more likely, and considerable indirect evidence was brought forth in support. As indicating a potentially important effect of epinephrine upon the brain, this hypothesis deserves our close scrutiny.

Evidence that epinephrine could stimulate adrenal cortical hormone release was first obtained by Vogt (262), who demonstrated an increase in the survival time of adrenalectomized rats treated with plasma from the adrenal vein of dogs receiving an intravenous infusion of epinephrine (7 to 226 μg over 6 to 20 minutes), as compared with those treated with adrenal vein plasma in the absence

of the epinephrine infusion. The following year, Long and Fry (136) demonstrated a fall in adrenal ascorbic acid following 200 μg/kg of epinephrine subcutaneously or intravenously in rats; the effect was absent in hypophysectomized animals, and they concluded that this fall was an expression of pituitary ACTH and cortical hormone release. Subsequent attempts to find the minimal effective dose showed that an intraperitoneal or intramuscular infusion of 3 μg/kg per hour in the rat could produce a significant adrenal ascorbic acid fall; if given more rapidly, it required more to be effective. Estimations of the threshold dose intravenously were unsuccessful since even saline had an effect by this route (73). Munson and Briggs (183) found total doses of 10 to 20 μg effective in rats intraperitoneally, but could detect no fall in adrenal ascorbic acid from single intravenous injections of 0.25 to 20 μg/kg, the higher doses being fatal. Comparatively direct evidence of rapid ACTH release into the bloodstream was obtained by Farrell and McCann (65) from injections of epinephrine (1.25 to 10 μg total dose) intravenously in rats; blood from such rats produced a fall in the adrenal ascorbic acid of hypophysectomized recipients, while epinephrine alone lacked such an effect.

Recant *et al.* (205) published an extensive series of studies on eosinopenia induced by ACTH, cortisone, and epinephrine in man, dog and rat. They found that cortisone was able to produce eosinopenia directly, in the absence of pituitary and adrenal, but that ACTH eosinopenia required the presence of the adrenals. Epinephrine could produce eosinopenia only in the presence of adrenals, pituitary and anterior hypothalamus, and they naturally concluded that epinephrine acted indirectly to produce pituitary ACTH release, probably by affecting the hypothalamic controlling centers. The importance of adrenals and pituitary for epinephrine eosinopenia was confirmed in the mouse (249). Norepinephrine seemed to have a much weaker eosinopenic action than either natural or synthetic epinephrine (107, 145). Since the eosinophil count is easily performed, repeatable and harmless, it was seized upon by a number of investigators and forms the basis for a great number of papers purporting to study ACTH control; for this reason it deserves special attention.

That epinephrine-induced eosinopenia need not be due to activation of the pituitary-adrenal axis was first shown by Muehrcke *et al.* (182), who produced a substantial eosinopenia from 0.3 mg of epinephrine subcutaneously in patients with bilateral adrenalectomy and orchidectomy maintained on cortisone. This has subsequently been confirmed for hypophysectomized man as well (105). Next Henry *et al.* (92) studied epinephrine eosinopenia in adrenalectomized dogs; the eosinopenic response was present when the dogs received an adequate maintenance dose of cortisone, but disappeared or was replaced by an eosinophilia if the cortisone was withdrawn. They postulated that epinephrine produces its eosinopenia directly, but that a certain background of 11-oxysteroids must be present in an essential but solely permissive (110) role.

With the advent of techniques to measure directly the 17-hydroxy-11-oxysteroid content of plasma and urine, it soon became apparent that epinephrine does not in fact usually produce any rise in the levels of these hormones. Thus

administration of epinephrine in adequate dosage intravenously or subcutaneously to man generally fails to increase either the plasma or urinary corticoids, even though producing a marked eosinopenia (62, 108, 116, 121, 187, 207, 220). In the dog, epinephrine fails to increase the blood corticoids and may even produce a drop (186). Likewise, 200 μg/kg has been ineffective in rats (9); 200 μg total dose is ineffective in the guinea pig, although larger doses may produce some response (40). Of additional interest is the observation that the eosinopenia from intravenous ACTH tends to reach its maximum after 3 to 4 hours, while that from epinephrine is already maximum at 2 hours (108), making it extremely unlikely that epinephrine eosinopenia is due to a subsequent ACTH release.

Reevaluation is necessary of studies in which eosinopenia was the sole index of ACTH release: For example, it has been shown in rats that the 1-hour eosinophil fall to cold, insulin, laparotomy, or histamine is greatly reduced or abolished after adrenal demedullation although the 4-hour drop may persist (135, 144). It is also impaired or abolished by lesions of the brain or spinal cord which interrupt central sympathetic pathways (32). After transection of the spinal cord above the adrenal outflow, cephalic pain fails to produce the usual 1-hour eosinopenia (135). While all this was originally interpreted as indicating epinephrine discharge must be the essential first step leading to ACTH release and adrenal cortical activation from stress, it is now more likely that the 4-hour eosinopenia simply represents a direct action of epinephrine and will naturally be diminished or absent in all the above experimental situations; even the 1-hour eosinopenia need not necessarily be due to ACTH release. Likewise, the abolition of epinephrine eosinopenia reported in dogs with diabetes insipidus (247), after hypothalamic lesions (106) or pituitary stalk-section (217) need not be interpreted as an interruption of an epinephrine-hypothalamus-pituitary-adrenal cortex chain; it is more likely due to a chronic insufficiency of corticosteroids in these animals, with inadequacy of the permissive hormonal effect, especially since in the latter experiments epinephrine eosinopenia was restored with doses of cortisone which did not in themselves cause eosinopenia. The same interpretation may also hold for the abolition of epinephrine eosinopenia in cats or rats after hypothalamic or median eminence lesions (130, 142, 197).

To evaluate the role of the adrenal medulla in the ACTH response to stress, a number of experiments have been performed in which this organ was eliminated by demedullation or denervation; only a few of these can be cited. One month after adrenal demedullation, Gordon (80) found that the adrenal ascorbic acid fall from insulin, histamine and cold was present and intact. In reviewing her own work and that of others, Vogt (263) showed that the adrenal medulla played no demonstrable role in the ACTH response to physical stress (cold, histamine, hemorrhage, formalin, etc.) and only a small and unessential one in the ACTH response to emotional stress; at the same time, she pointed out the difficulties of using the ascorbic acid fall in demedullated glands because of the great variability of their ascorbic acid content. Using specific pharmacologic blocking agents Guillemin (86) concluded that neither epinephrine nor norepinephrine could be indispensable links in the chain of ACTH-release to nonspecific stress.

Epinephrine depression of adrenal ascorbic acid and cholesterol in rats remains to be explained. The usual dosage (200 μg/kg) is quite high (136); norepinephrine is less effective (185, 208), while paredrine, *p*-sympatol and amphetamine are even less potent (185, 191). It may be that epinephrine can exert some direct stimulating effect upon the adrenal cortex provided that the latter has not been allowed to atrophy after hypophysectomy (167, 195); the adrenal ascorbic acid fall may be a more sensitive index of adrenal cortical stimulation than measurable elevation of plasma or urine hormone levels, particularly if the ACTH response is very transient; or epinephrine may directly depress the ascorbic acid and cholesterol content of the gland without affecting hormone production, since these determinations are indirect indicators of hormone production at best. Dissociation of ascorbic acid fall and adrenal corticosteroid release has been observed in rats after hypothalamic lesions (248). The resolution of this problem is clearly outside the scope of this review.

In summary, there is no evidence that moderate doses of epinephrine cause the release of ACTH in man, dog or guinea pig as measured by plasma or urinary corticoid levels. Evidence for such release in the rat is based on an indirect index, the adrenal ascorbic acid fall, and the doses used generally exceed the physiologic range. Moreover, the adrenal medulla is unessential to the ACTH response to stress. Epinephrine-induced eosinopenia in most or all instances is a direct effect of epinephrine requiring the presence of cortical steroids. In the light of these findings there is no present need to postulate stimulation by epinephrine under physiologic conditions of hypothalamic centers concerned with the control of pituitary ACTH secretion, although it may occur in certain species after large doses. While the observation that epinephrine can affect the electrical activity of the posterior hypothalamus in cats and monkeys (196) was originally interpreted as stimulation of specific hypothalamic-pituitary mechanisms, it now seems more likely to be part of a more general action of epinephrine on the reticular activating system (see III,F).

3. Gonadotropins and ovulation. After previous elimination of the cervical sympathetics, vagi, and petrosal nerves as sources of the hypophysial control leading to ovulation, its successful production from stimulation of the hypothalamus and pituitary stalk region in the rabbit naturally centered interest on these structures (88). Subsequent comparison of the electrical thresholds of hypothalamus and pituitary indicated that it was the former, not the latter, which was actually electrically excitable, and a humoral rather than a neural link was suggested as the means by which the hypothalamus influenced the anterior pituitary to release LH and thus induce ovulation (151). Soon thereafter, it was observed that the adrenergic blocking agent Dibenamine could prevent postcoital ovulation in the rabbit provided that it was given within 1 to 3 minutes afterward (229). Likewise, Dibenamine administered to 4-day cyclic rats at the proper time on the day of proestrus blocked ovulation in this species as well (64). Injection of epinephrine directly into the pituitary gland of etherized rabbits resulted in ovulation in 30 to 50% of instances (152), and instillation of epinephrine or norepinephrine into the third ventricle of rabbits also had this effect (222). Con-

sequently, epinephrine or a like substance was suggested by these authors as the possible humoral link.

Since then the story has been considerably complicated by the findings that ovulation can be blocked also by atropine (230), Nembutal (63), SKF-501 (227), methantheline (Banthine) (228), morphine (12), chlorpromazine and reserpine (11) and alcohol (224), but not by tolazoline (Priscoline), 2-dibenzylaminoethanol, phentolamine (Regitine), tetraethylammonium, procaine, thiopental, pyrilamine (Neo-Antergan), or curare. To explain the action of atropine and Banthine, an additional cholinergic link was postulated by these same authors; it was placed somewhat proximal to the adrenergic link both in space and time. An additional mechanism, vulnerable to pentobarbital was presumably even more proximally situated, since it blocked ovulation in the rat when it could be given prior to neurogenic stimulation but not in the rabbit after (by even a few seconds) the coital stimulus. Subsequently a parallel was drawn between the capacity of atropine, morphine and pentobarbital to produce deactivation of the EEG and raise the electrical threshold of the reticular activating system, and the possibility that these drugs prevented ovulation by acting upon this system was suggested (226). It has also been shown that these same three drugs can prevent ovulation induced by electrical stimulation of the hypothalamus unless the electrodes are within or very close to the median eminence itself (221). On the other hand, reserpine and the adrenergic blocking agent SKF-501 cannot block ovulation from hypothalamic stimulation, and the latter is not known to affect the reticular activating system, so that a different site of action was postulated for these agents (221, 226). Finally, ovulation from instillation of epinephrine into the third ventricle can be blocked by Dibenamine, SKF-501, atropine and pentobarbital, but not by destruction of the mesencephalic reticular formation; see the review by Sawyer, 1958 (224).

The neuropharmacology of ovulation is obviously complex indeed. It is the purpose of the present review only to evaluate the role played by centrally-acting epinephrine in these mechanisms. Certain objections come at once to mind. With respect to the local injection experiments, it is unsettled whether both the anterior pituitary gland and the hypothalamic structures bordering the third ventricle are sensitive to epinephrine, or whether the epinephrine can diffuse from one to the other no matter where it is injected, in which case it remains an open question which of the two is the sensitive structure. Donovan and Harris (58) repeated the local injection of epinephrine into the anterior pituitary gland and concluded that its ovulatory stimulus was nonspecific, and related to the pH of the solution and the rate and volume of the injection, rather than to the presence of epinephrine. Moore (181) has observed that doses of Dibenzyline and Dibenamine which block ovulation in rats also cause a fall in adrenal ascorbic acid, presumably from ACTH release. By administering these drugs daily for 12 or more days, the nonspecific stressing effect wore off but the adrenergic blockade persisted. In these rats ovulation resumed. He concluded that the ovulation-blocking effect of these drugs was due to temporary shift of pituitary activity from gonadotropin to ACTH release. Perhaps re-

lated is the fact that much of the adrenergic blockade produced by these drugs comes on slowly (188), whereas ovulation is blocked within a minute of their intravenous administration. Moreover, the potent adrenergic blocking agents Priscoline and Regitine lack the capacity to prevent ovulation altogether, although it is uncertain that they can pass the blood-brain barrier. Lastly, intravenous and intracarotid epinephrine and norepinephrine consistently fail to induce ovulation themselves (152, 225).

In conclusion epinephrine or norepinephrine injected into the anterior pituitary gland or third ventricle can produce ovulation, but their administration by the intravenous or intracarotid route is ineffectual. The essential locus of action, pituitary or hypothalamus, cannot be determined at present and the specificity of action, at least on injection into the pituitary, has been disputed. The capacity to block natural or artificially induced ovulation is shared by a number of drugs, including cholinergic blocking agents, sedatives and anesthetics, and some adrenergic blocking agents but not others. Whether those adrenergic blocking agents which are effective work by virtue of their intrinsic adrenolytic properties or through a nonspecific stressing effect is also unsettled at the moment. The facts remain, however, that intraventricular epinephrine can induce ovulation, even after destruction of the upper brain stem, and that this ovulation can be prevented by a variety of pharmacologic agents likely to affect central synapses. The interesting suggestion has been made (224) that this effect is mediated through adrenergic mechanisms within the hypothalamus, where epinephrine and norepinephrine are abundantly present (266). This important possibility is still unproved, however, and will require further study. In the meantime, it may not be amiss to point out that no drug has a single action, and that in the investigation of brain mechanisms pharmacologic agents are double-edged swords to be employed with caution.

D. Electroencephalogram

References to the electroencephalographic effects of epinephrine are of necessity scattered throughout this review, particularly in the section on the reticular activating system. A brief summary of the electroencephalogram (EEG) changes, especially in man, will serve, however, to gather these data in one place for consideration. In 1949, Toman and Davis (256) in their review on the effects of drugs on the electrical activity of the brain stated: "The attention given to the action of epinephrine upon the EEG has been disproportionately small in comparison to that lavished upon the more popular neurohumor acetylcholine . . ."; they quoted only two references on epinephrine and several more on amphetamine.

Gibbs *et al.* (74) noted no EEG effect in man from 0.5 to 0.8 mg of epinephrine intravenously. In the hands of Grinker and Serota (84) the same dose produced excessive beta activity, but the subjective complaints were so severe that they switched to intramuscular administration, where they noted the same changes but to a less degree; schizophrenics showed less EEG change and subjective reaction than normals. Using frequency analysis, Gibbs and Maltby (75) noted a shift towards the faster frequencies from epinephrine, whereas another group

(83) giving 0.05 to 0.1 mg intravenously noted an intensification of the alpha rhythm or the appearance of slow waves. Slow waves were also seen after subcutaneous injection by Faure (66). More recently, small intramuscular injections (0.2 mg) were found to produce only minor and nonspecific changes in the EEG (81). Intravenous injection of norepinephrine (18 to 32 μg) to normal and schizophrenic subjects produced a brief EEG activation after a 20 to 30 sec latency. A much higher proportion of the normals (9/13) showed this effect than did those with schizophrenia (4/18) (273). As already mentioned, intraventricular injections of epinephrine in man produce an increase in alpha rhythm or even the record of normal sleep (244). Dureman and Scholander (61) studied the effect of intravenous epinephrine on habituation of the arousal reaction to sound in medical students. Once they had become habituated, infusion of epinephrine (0.1 μg/kg per min) tended to restore their activation pattern from the sound, due, the authors suggested, to facilitation of arousal mechanisms.

In the cat sleeping normally, intravenous doses of epinephrine (2 to 5 μg/kg) produce EEG activation, but once the animal is awake, no further change is seen from additional injections; when the EEG reverted to the sleep pattern, the threshold of EEG activation to epinephrine was then raised for several minutes (219). In the unanesthetized acute preparation immobilized with curare, intravenous epinephrine of the same order of dosage will produce EEG activation if the EEG is naturally deactivated to begin with. If deactivation is artificially produced by brain stem section or coagulation, epinephrine is still effective in producing EEG activation, but if deactivation is produced by anesthetics, even in small amounts, epinephrine no longer has any effect, or produces the opposite, namely slow waves (22, 212). This latter effect can be reduced or eliminated by section of the moderator nerves (22, 184).

Intracarotid epinephrine (1 to 250 μg) in waking cats produced no change (218), or some further EEG activation (137). Intraventricular epinephrine in dogs produced no change (131, 132), and led to EEG-behavioral dissociation in cats (219) in which the EEG was activated but the cat prostrate and apparently unconscious.

In summary, adminstration of clinical dosages of epinephrine to man subcutaneously or intramuscularly probably has no specific EEG effect. Intravenously, it can produce an increase in the EEG frequency or increased beta activity, sometimes preceded by slow waves. In experimental animals, moderate doses given intravenously produce EEG activation, provided the EEG background is suitable to reveal it and provided the animal is unanesthetized. If anesthetized, small doses do nothing, larger doses produce slow waves, mainly through inhibition of the brain stem through the moderator nerves (see II, D). Intraventricular epinephrine in comparatively large doses leads to remarkably little EEG change even when behavior is profoundly modified.

E. Cerebral cortex

Several years after his demonstration that epinephrine exerted an inhibitory effect upon peripheral autonomic synapses, Marrazzi (157) studied its effect

upon evoked potentials of the visual cortex produced by light flashes or direct stimulation of the optic tract in the lightly anesthetized cat. He reported a reduction in these potentials from epinephrine and amphetamine, and noted the same effect upon auditory cortex evoked potentials as well. He subsequently reported the effect of such agents upon the transcallosal response (54), in which an area of cortex (usually visual) of one hemisphere is stimulated and the evoked electrical response in the homologous area of the opposite hemisphere recorded. Drugs were generally injected into the carotid artery ipsilateral to the recording site. Again, a diminution of the recorded potential was observed from epinephrine (10 μg), while acetylcholine had the opposite effect, augmentation (164). Subsequent observations showed that diminution of these potentials could also be produced by amphetamine (162), mescaline (89), LSD-25 and serotonin (163), bufotenine, norepinephrine, and adrenochrome (158). More recently, Marrazzi reported that moderate doses of the tranquilizing agents chlorpromazine and reserpine could prevent the changes in the transcallosal response produced by epinephrine, although larger doses of these drugs themselves reduced the response (158). If ranked in order of increasing potency, mescaline is weakest and adrenolutin, adrenochrome and norepinephrine are in the same range. Epinephrine and LSD-25 are moderately potent, while serotonin and bufotenine are the most active of all, bufotenine being 10,000 times more effective than mescaline (160). Marrazzi has interpreted these findings as being due to a blocking or inhibiting action of epinephrine and other adrenergic substances upon the cortical synapses involved in the transcallosal and specific evoked response. Because he feels that inhibition is the principal and specific action (as opposed to nonspecific postinhibitory facilitation) of epinephrine on peripheral (autonomic) synapses, he has come to regard epinephrine as having a general inhibitory effect, opposed to or counterbalancing, as it were, the stimulatory effects of acetylcholine at both central and peripheral synapses. Serotonin, another naturally-occurring possible neurohumor, is considered to have a similar but more potent effect. More recently he has taken into account the apparently stimulatory central effects of epinephrine in certain circumstances with the suggestion that epinephrine may depress certain inhibitory neurones, thereby releasing others, resulting in the appearance of overactivity (158–161).

Perhaps the greatest difficulty in evaluating the findings and hypotheses just summarized is the present chaotic state of cortical electrophysiology itself. The transcallosal response employed so extensively in the above experiments was originally thought to represent a simple two-neuron arc, with the surface-positive wave representing the presynaptic impulse entering the cortex from the opposite side (input), and the succeeding surface-negative wave an indication of the postsynaptic impulse presumably leaving (output). Thus diminution in the amplitude of the surface-negative component without change of the preceding surface-positive wave was taken as evidence that the synapse had been inhibited. Much work is presently in progress, employing advanced techniques of laminar microelectrode analysis, in the study of the transcallosal, specific evoked, and direct cortical responses as well as the EEG, and the interpretation given above is no longer

certain, although not necessarily incorrect; see discussion by Peacock (193). The surface-positive wave, for example, could be the expression of a postsynaptic event, specifically the postsynaptic potential of the soma of neurones lying in the deeper layers of the cortex, although axosomatic endings in this fiber system are believed to be sparse. The surface-negative wave might be postsynaptic in origin and related to axodendritic rather than axosomatic synapses, although the possibility of surfaceward decremental conduction in apical dendrites must also be considered. It has been suggested that even the surface-negative wave might be presynaptic and produced by the myelinated-unmyelinated terminals of the entering fibers acting as stationary dipoles in the depths (193). While the surface-negative wave may be due to a postsynaptic potential arising at superficially lying axodendritic synapses, this does not necessarily involve the same cells as those responsible for the surface-positive wave. Moreover, although the amplitude of the surface-negative wave may be reduced, there is no way of knowing whether this involves excitatory or inhibitory synapses, or both, and thus no way of predicting the ultimate effect on cortical activity. There is probably no point in trying to relate the action of drugs to specific cortical structures until there is more general agreement upon the meaning of the electrocortical events used in their study.

While it still remains possible that the diminution in the surface-negative wave does represent some sort of synaptic inhibition (using the term in a very restricted sense), to say that epinephrine inhibits the cerebral cortex generally would be distinctly misleading. For example, injections of epinephrine (up to 250 μg/kg) into the carotid artery of the freely moving cat with implanted carotid catheter and cortical electrodes (216) produces no detectable neurologic deficit and no alteration of the already activated EEG (218). This preparation has been shown to be very sensitive to drugs which interfere with neural function, for it manifests motor weakness, EEG changes, and a homonymous visual field defect with doses of barbiturates too small to have general effects. While subtle perceptual aberrations from epinephrine could of course be missed, the total lack of behavioral or electrical change is striking. Infusions of epinephrine (1 to 10 μg/min) into the carotid arteries of unanesthetized patients produced no focal neurological defects or subjective effects (51). A diminution in the transcallosal response also accompanies EEG activation from stimulation of the reticular formation (202), an event generally associated with arousal and motor facilitation.

Finally, the doses of epinephrine (10 μg) and norepinephrine (150 μg) injected into the carotid artery to produce the changes in the transcallosal response are very high and far exceed the physiological range, although without knowing the volume and speed of injection, the factor by which they exceed the same dose given intravenously is difficult to estimate, perhaps 10 to 100. Moreover, the specificity of the response is rather low, since it has been described for the catecholamines, their phenyl derivatives, indoles like serotonin and adrenochrome, γ-aminobutyric acid, and even the tranquilizers previously referred to, and the most potent members (bufotenine and serotonin) are not adrenergic at all in the usual sense of the term.

Minz and his associates have published a series of papers dealing with the action of epinephrine upon various aspects of cortical activity, beginning with the observation that the duration of induced seizures in rabbits is prolonged by 5 to 50 μg/kg of epinephrine (171), an effect at least partly related to the elevation in blood pressure (5). For some curious reason, it was necessary to thyroidectomize most of the rabbits to bring out this effect. Subsequently, a similar effect was described in the acute, unanesthetized spinal cat, in which seizures induced by cortical stimulation were markedly prolonged by the administration of 1 to 10 μg of epinephrine or norepinephrine, the two being about equally potent (174). In the anesthetized monkey, application of 1/1000 epinephrine directly to the motor cortex produced an increase in the mechanical and electrical after-discharge from stimulation, and a 30% reduction in the threshold for induced movement, at the same time diminishing the spontaneous cortical activity (179, 180). Goldstein and Minz (79, 175) have studied the effects of local and intravenous epinephrine upon a particular aspect of cortical electrical activity referred to as "tensioactivity," a figure derived by dividing the summed voltages of the EEG during a period of time by the frequency during that period. These investigators find a normal gradient in tensioactivity in the rabbit cortex, and are able to increase the index and alter the gradient with 10 μg of epinephrine intravenously, or by applying 5% epinephrine directly to the cortex. While quantification of the EEG is certainly very desirable, the writer is unable to interpret changes in this particular index (tensioactivity) or to relate them to conventional EEG patterns and their neurophysiological or behavioral counterparts. Furthermore, the amount of change (53.55 ± 2.34 before epinephrine and 56.04 ± 1.76 after), while statistically significant, is not very impressive. Recently Minz *et al.* have suggested that at least part of the EEG effect of local epinephrine is not direct but due to the secondary liberation of oxytocin from hypothalamus and pituitary (see below). They have reported an increase of tensioactivity from oxytocin alone, and both oxytocin and vasopressin block the effects of epinephrine applied directly to the cortex. They were able to reproduce the effects of cortically-applied epinephrine by a mixed intravenous injection of one part of Pitocin and two parts of Pitressin (176, 177).

In 1953, this same group began a series of experiments on an interesting and previously unrecognized phenomenon, *i.e.*, that the local application of concentrated (5 to 10%) epinephrine to rabbit cortex could produce an elevation of blood pressure (172). Further work has demonstrated that only certain cortical areas will produce this pressor response. Ablation of the cortex and application of the epinephrine to the underlying white matter is without effect, as is contact of the epinephrine with other cortical areas, dura, muscle, etc. With repeated applications, the cortex becomes sensitized so that concentrations previously too weak (2%) become effective, and the responsive area of cortex gradually enlarges. Surprisingly enough, the response persists after adrenalectomy, section of the spinal cord at C6, division of the pituitary stalk or hypophysectomy, section of the corpus callosum and anterior commissure, or removal of both occipital poles of the brain. On the other hand, it is abolished by destruction of or a transverse

section through the hypothalamus. In suitable preparations, they could demonstrate antidiuresis and increase in the activity of the estrogen-primed uterus at the same time as the pressor response, and concluded that the hypothalamus was releasing pressor, antidiuretic and oxytocic hormones together. Moreover, the pressor response could be selectively eliminated by an acute anterior hypothalamic lesion, while the oxytocic response was selectively prevented by a posterior hypothalamic lesion. Chlorpromazine blocks the response while reserpine increases it. They concluded that epinephrine applied to certain cortical areas activates a pair of pathways, one going to the anterior hypothalamus and causing vasopressin release, the other going to the posterior hypothalamus to cause the release of oxytocin (42–49, 170, 173).

Since it is already well known that the hypothalamus contains both vasopressin and oxytocin (100, 265) and probably produces them in the supraoptic and paraventricular nuclei, sending them to the neurohypophysis for storage and release (10), their discharge from the hypothalamus after removal of the pituitary is at least possible. It is rather surprising that this work has not aroused more attention or efforts to confirm it. It is also surprising that epinephrine (in these admittedly very high concentrations) is able to induce a response when electrical stimulation or other pharmacologic agents presumably are not. Lastly, it has been assumed up to now that while the hypothalamus may manufacture vasopressin and oxytocin, their storage and release is a function of the neurohypophysis, which was eliminated in some of the above experiments. The amount of hormone in the brain is much less than that in the pituitary, making it difficult to understand why hypophysectomy or stalk section has so little effect on the response. If these findings can be confirmed, they will add an important item to the list of functions excitable by centrally-acting epinephrine, although the specificity of such high concentrations must remain questionable. Moreover, they will indicate that the hypothalamus can function as a release site as well as a manufactory of its hormones. They would also furnish support to the growing list of evidence suggesting that the cerebral cortex is no more homogeneous pharmacologically than it is biochemically, histologically or electrically.

In summary, epinephrine in rather large doses is able to reduce the surface-negative wave of the transcallosal cortical response in the anesthetized cat. Norepinephrine is less potent, while serotonin and bufotenine are much more so, and other agents including γ-aminobutyric acid and certain tranquilizers also show this effect. Although inhibition of an axodendritic cortical synapse is a reasonable explanation for this effect, it is not proved, nor can this effect be interpreted yet in terms of over-all cortical activity. Doses of epinephrine which produce the above effect are without behavioral, neurological or EEG influence in the unanesthetized and freely moving animal. Epinephrine applied locally to the cortex in rather high concentrations lowers the threshold for electrically induced cortical movement, prolongs the afterdischarge from such stimulation and prolongs artificially-induced seizures. It also diminishes spontaneous activity locally and alters the EEG generally. At least part of this latter effect has been ascribed to the secondary liberation of neurohypophysial hormones. Pressor, ox-

ytocic and antidiuretic effects have been produced from local application of epinephrine to certain areas of the rabbit cortex, believed due to release of these factors from the hypothalamus.

F. Brain stem and reticular activating system

In 1954, Bonvallet, Dell and Hiebel reported that intravenous epinephrine was capable of producing EEG activation in the cat. The effect is clear-cut and the doses of epinephrine required are not excessive, and one might well inquire why such an effect had not been reported long previously. As will be described below, elicitation of the response requires that the preparation be unanesthetized, in good condition, with an EEG record not already activated to begin with—a rather critical set of circumstances not easy to obtain. Further investigation of the phenomenon has proved quite profitable and the description to be given below represents the findings of Dell and his colleagues plus some confirmatory and additional experiments of the writer, some unpublished (22, 55, 212–215).

Intravenous injections of 2 to 8 μg/kg of epinephrine produce a characteristic EEG activation, beginning approximately after a 10 to 12 sec latency and lasting 10 to 50 sec, depending on the dose. Provided several minutes are allowed to elapse, this can be repeated over several hours. In order to detect the response, the EEG must be deactivated ("synchronous") to begin with. This can be obtained by preventing or eliminating pain, discomfort or distraction of the animal, which is then maintained on curarizing agents, but spontaneous fluctuations in the EEG are difficult to eliminate and the method is tedious. Artificial deactivation of the EEG provides a more useful preparation and can be produced by section of the brain stem or electrolytic coagulation of the reticular core at about the ponto-mesencephalic junction. In such a preparation, the EEG is constantly deactivated (similar to Bremer's *cerveau isolé*). Spontaneous or accidental variations are eliminated and the pharmacologic threshold remains quite stable. In our experiments, the acute EEG activation was also produced by norepinephrine, which within the limits of the method seems to have the same potency. Phenylephrine is only one-third as potent; methamphetamine will also produce the response but is much less effective and shows tachyphylaxis.

It is difficult to exaggerate the sensitivity of the response to anesthetics. Ether, barbiturates, alcohol, and chloralose all block the response in considerably less than anesthetic doses. With the shorter-acting agents this is reversible. The response will also disappear if the preparation is allowed to deteriorate from low blood pressure, hypothermia, etc.

Various experiments have been undertaken to determine at what point the epinephrine acts to produce this EEG effect, and attention naturally turns to the reticular activating system, where electrical stimulation has the same effect. If the brain stem is progressively destroyed working rostrad, the response disappears at about the posterior border of the diencephalon, and the electrical reaction of the hypothalamus to epinephrine described by Porter (196) also shows a similar dependence upon integrity of the brain stem (198). Partial destruction of the midbrain reticular formation tends to produce a rise in the threshold roughly

proportional to the extent of destruction, and unilateral destruction abolishes the EEG activation only ipsilaterally. On the other hand lesions of the pons may actually increase the preparation's sensitivity to epinephrine, a phenomenon to which we shall return later. It is obvious from all this that the response is independent of the spinal cord, lower brain stem, and cranial nerves 5 and below.

Microelectrode recordings from reticular units in both the intact preparations and in the isolated midbrain slab showed that the firing rate of these units could be influenced by epinephrine. Some neurones responded by an increased rate of discharge, in others the firing rate decreased; still others were unaffected (23). Using a similar technique in the decerebrate cat, Bradley and Mollica (30) also found units in the mesencephalic and bulbar reticular formation which responded to epinephrine and norepinephrine with either an increase or a decrease in discharge rate. Intracarotid injections were effective in smaller doses than intravenous ones, and showed shorter latency effects preceding any change in the blood pressure. They suggested that there are both adrenergic and nonadrenergic neurones in the reticular formation; some of the latter likely to be cholinergic.

Further efforts at localization were made by the writer who injected 1 μg amounts of epinephrine directly into the brain stem under stereotaxic guidance (213). EEG activation was obtained from regions of the midbrain reticular formation which correspond almost exactly with similar maps made from electrical stimulation, whereas injections into the peduncles, periaqueductal gray matter and colliculi were without effect. The application of this method is limited by the fact that certain neurones are excitable by mechanical or osmotic stimuli (4, 206, 250) and it is difficult to be sure to what extent the stimulation is due to these factors and how much due to the epinephrine *per se*; reference to this problem has already been made in III, C, 3. In the case of the midbrain, saline control injections in the same or symmetrical points rarely had any effect, but in a similar attempt to map the hypothalamus considerable response to control injections was encountered, and excitation of the hypothalamus from saline injections, hypertonic or isotonic, has already been reported (250).

Dell *et al.* (55) also studied the effects of epinephrine upon the descending reticulo-spinal system. They recorded the electrical activity of the ventral roots in response to dorsal root volleys and found facilitation of both mono- and polysynaptic reflexes. This system was stimulated by epinephrine in approximately the same dosage, and showed the same vulnerability to anesthesia and dependence upon the mesencephalic-hypothalamic segment of the brain stem. Sigg *et al.* (246) found that epinephrine (1 to 20 μg intravenously) augmented cortically induced movement and the patellar jerk in lightly anesthetized cats. Deepening the anesthesia abolished this effect or converted it into inhibition. Lesions in the posterior hypothalamus abolished epinephrine facilitation of both the reflex and cortically-induced movements, but the inhibition seen with larger doses of epinephrine and under deeper anesthesia persisted even in the spinal preparation. They concluded that epinephrine mediates its facilitatory effects through the reticular activating system-hypothalamus, but that inhibition can take place at cord levels.

The effects of epinephrine upon the reticular activating system are not purely excitatory, however, even in the unanesthetized preparations described. One of the major sources of inhibition of the reticular formation is that via the four moderator nerves (22, 55, 184), produced by the effects of epinephrine upon the baroreceptors directly and through the elevation in blood pressure, and to which reference was made in II, D. Even after this source has been eliminated, however, the fact still remains that preparations may become *supersensitive* to epinephrine EEG activation after lesions restricted to the pontine reticular formation, suggesting some inhibitory activity, perhaps also adrenaline-sensitive, present normally at the pontine level (22, 198, 212). This may be related to current work attempting to evaluate the importance of the various inflows which maintain EEG activation in the *encéphale isolé*. The fifth nerves have been found to be a major source of this activation, and their transection frequently results in prolonged EEG deactivation (210). However, it is possible to obtain sustained EEG activation by certain critically placed brain stem sections *above* the level of the fifth nerves, again suggesting release from a tonic inhibitory influence originating at the pontine level (211).

DeMaar and Martin (56) have reported EEG activation in acute, unanesthetized spinal cats from epinephrine. It was effective in only half of their series of 40 cats, and norepinephrine was not effective at all. The spinal cat (*encéphale isolé*) is a rather unsuitable preparation to use in this sort of study, however, since its blood pressure is low and extremely sensitive to the pressor effects of catecholamines (significant pressor responses to as little as 5 to 10 mμg, in the writer's experience). Also its general condition deteriorates with time, due to the low blood pressure, loss of temperature control, etc. All this tends to exaggerate the importance of the inhibitory effect upon the reticular formation via the baroreceptors and to lessen sensitivity to the direct excitatory effect of epinephrine. The lack of response to norepinephrine is difficult to understand, but may be related to the greater pressor potency of this agent. Further quantitative comparison between epinephrine and norepinephrine on these and other central effects needs to be done, in which case it may be possible to decrease the error of the method by employing constant intravenous infusions rather than single intravenous injections. Also using the *encéphale isolé*, but with the baroreceptors denervated, Mantegazzini *et al.* (149) observed EEG activation from both epinephrine and norepinephrine synchronous with the rise in blood pressure. They found that intracarotid or intravertebral injections were no more effective than intravenous ones, leading them to consider an indirect action of epinephrine through pressor or metabolic effects as more likely than a direct one.

Some studies have also been made on the effects of epinephrine upon certain reflexes involving the brain stem. In cats anesthetized with chloralose, 3 to 300 μg/kg of epinephrine intravenously regularly increased the linguomaxillary reflex. This effect was blocked by atropine, suggesting the participation of cholinergic mechanisms (24). Stimulation of the dorsomedial medullary reticular formation produced inhibition of the patellar and facilitation of the linguomaxillary reflex, and injections of epinephrine or norepinephrine diminished this effect

(178). Apparently opposite results have been obtained recently by Cranmer and Bach (52) in experiments showing that the inhibition of the patellar reflex from medullary stimulation could be blocked by administration of Dibenzyline and restored by an infusion of epinephrine. They were also able to lower the electrical threshold of certain inhibitory points in the medulla by microinjections of epinephrine into the same site, whereas in other areas such injections had no effect.

In summary, moderate intravenous doses of epinephrine and norepinephrine simulate many of the effects of electrical stimulation of the brain stem reticular formation, including EEG activation, spinal motor facilitation and certain reflex effects involving the brain stem. Much evidence strongly indicates that the epinephrine acts directly upon the brain stem itself, in particular the mesencephalic reticular formation and posterior hypothalamus, to produce these effects which are reflected in spinal cord activity and the EEG. The facilitation is very susceptible to anesthetics, under the influence of which it may disappear revealing an underlying inhibition which is partly reflex through the moderator nerves. Part of the inhibition is not reflex, however, but direct and suggests that epinephrine stimulates several different brain stem mechanisms, the end-effects of which may be mutually opposed. In the unanesthetized preparation, facilitation predominates.

G. Adrenergic potentiating and blocking agents

Although not strictly within the compass of this review, adrenergic potentiating and blocking agents contribute so much to our knowledge of catecholamine action that there is some justification for considering them, however briefly. In 1953 it was reported that amphetamine produced EEG activation in dogs (231) and cats (29), accompanied by indications of arousal, increased motor activity, and even excitement. The latter authors found that the effect persisted in the *encéphale isolé*, but disappeared in the *cerveau isolé*, and they postulated that amphetamine produced its EEG and behavioral changes by an action upon the brain stem. Similar results were reported by Hiebel *et al.* (98), who found that Maxiton appeared to stimulate the reticular formation and to increase its responsiveness to sensory stimuli and epinephrine. The dependency of amphetamine action upon the integrity of the mesencephalic reticular formation has since been confirmed in cats (214) and rabbits (138, 271).

Studying a selection of adrenergic agents, the writer divided them into three categories, depending on their effects upon the EEG of the unanesthetized cat with pontine reticular coagulation. Epinephrine, norepinephrine and phenylephrine activated the EEG quickly but briefly and had no further effect upon their own threshold or that of each other. Cocaine, on the other hand, had no immediate EEG-activating effect, but produced a profound lowering of the threshold to EEG activation by epinephrine. With large enough cumulative doses, it produced a gradual but sustained EEG activation itself. Methamphetamine seemed to combine the properties of both groups in that it exerted a rather feeble immediate EEG activation showing tachyphylaxis, at the same time lowering the threshold to epinephrine and in large enough doses inducing a gradual

but sustained EEG activation. Their effects on the blood pressure and its response to epinephrine were quite similar. The first three were felt to act alike as congeners, whereas the last two were believed to act primarily or exclusively as sensitizing or potentiating agents. At other points in this review reference has been made to the effects of ephedrine on the spinal cord, of different sympathomimetics on analgesia, and of a variety of adrenergic agents on cortical evoked potentials.

Remarkably little work seems to have been done on the central actions of adrenergic blocking agents, either their direct effects or modifications they might induce in the nervous system's response to catecholamines. Furthermore, such effects as these agents do show have been attributed to properties they possess other than adrenergic blocking action itself. Dibenzyline, for example, prevents the ovulatory response to intraventricular epinephrine in the rabbit, and on the assumption that Dibenzyline is acting centrally, an adrenergic mechanism in the hypothalamus controlling ovulation has been postulated (III, C, 3). Dibenzyline will also prevent the lethargy and weakness produced by large subcutaneous doses of epinephrine in oil in rats (128), but these authors assumed that Dibenzyline acts only peripherally and then concluded that the syndrome of lethargy and weakness was therefore caused by some peripheral action of epinephrine. This is trying to solve a single equation with two unknowns, because the site of action of neither is certain. Dibenzyline does seem to have central actions, however (188), including its modification of bulbar reticular influences upon the patellar reflex (52). The facilitation of the patellar jerk presumed due to stimulation of the reticular activating system by endogenous epinephrine was abolished by a 1% Dibenamine infusion (246). The writer has been able to reverse the pressor response to epinephrine with Dibenzyline without abolishing the EEG-activating effect, but it is planned to extend these experiments with larger doses and longer time intervals before it is concluded that Dibenzyline does not affect this central response.

Chlorpromazine is a potent adrenolytic agent with pronounced central effects too numerous to be reviewed here. Hiebel *et al.* (98, 99) found that chlorpromazine suppressed epinephrine EEG activation, presumably by an action on the reticular activating system itself. DeMaar and Martin (56) administered it to unanesthetized spinal cats and found that it blocked epinephrine EEG activation in 50% of instances. The writer has made comparable observations in cats with pontine coagulation and found that as the effects of chlorpromazine come on gradually (from an intramuscular injection), epinephrine EEG activation is progressively delayed and may finally disappear altogether only to reappear at the delayed time and then gradually revert to its normal latency. This action is quite unlike that of the anesthetic agents referred to previously, which simply suppress the activation response. Even when delayed, the EEG activation under these circumstances was often quite intense. Although a ready explanation for these findings is not at hand, it may well relate to a differential action upon the temporal sequences of the simultaneous excitatory and inhibitory brain stem effects of epinephrine already mentioned (215).

The tendency of chlorpromazine to deactivate the EEG, lower central sympathetic tone, lessen spinal facilitation, and decrease both clinical and experimental spasticity, as well as its general tranquilizing and soporific qualities have led to the repeated suggestion that it acts upon the reticular activating system. Opinion is not unanimous on this subject, however, as the afferent inflow to the reticular formation, the diffuse thalamic system and the rhinencephalon have also been suggested as its site of action. The subject cannot be pursued further here, except to emphasize that the drug in clinical dosages can modify or block the response of the reticular activating system to epinephrine; it shares this property with a number of anesthetic and sedative drugs.

H. Miscellaneous

To complete this section it remains only to list several additional effects which are probably mediated centrally but about which relatively little is known. Fifty μg of epinephrine intravenously in the cat anesthetized with pentobarbital will cause a small but apparently consistent increase in brain temperature (194), an effect considered to be independent of changes in blood flow or blood pressure. Amphetamine has a similar effect coming on more slowly and lasting longer. Intravenous epinephrine raises cerebral oxygen consumption (126) but norepinephrine lacks this effect, and neither has any effect on it after intramuscular administration in oil (240). Mephentermine by intravenous drip raised cerebral oxygen uptake by 22% but had no effect on blood flow (68).

Intravenous infusions of both epinephrine and norepinephrine increase respiratory minute volume in normal human subjects. This is not due to a general increase in O_2 consumption, which only epinephrine produces (270). Infusions into the carotid or vertebral arteries of patients undergoing cerebral angiography were no more effective than by the intravenous route, and the investigators concluded that the respiratory stimulation was therefore not central or related to any effect upon carotid chemo- or baroreceptors (51). We have observed prolonged respiratory stimulation in cats receiving epinephrine intraventricularly, from which place it is supposed not to escape into the general circulation (II, C), and have been forced to assume a central action (219). The central concentrations in our experiments must have been much higher than those attained by the intravenous or intraarterial infusions in man and the mechanism may be different. Hypertonicity alone will stimulate respiration, apparently acting through receptors in the region of the fourth ventricle (6), and our intraventricular solutions were hypertonic. The hypertonic effects lasted only a few minutes, however, while hyperventilation from intraventriclar epinephrine has been observed for hours, making it difficult to account for the effect on this basis. Apnea from intravenous injection of epinephrine is an old experimental observation, at least part of which is due to reflex inhibition of the respiratory center through the carotid and aortic baroreceptor fibers. More recent experiments by Hoff *et al.* (103) in which the baroreceptor pathways were eliminated still demonstrated respiratory inhibition in animals with the brain stem transected through the rostral medulla, and they concluded that epinephrine had a direct inhibitory effect upon the respiratory

center. Inhibition of phrenic respiratory potentials has been reported from epinephrine and related amines (129).

Leimdorfer has made the interesting observation that intrathecal epinephrine will produce a rise in blood sugar in cats, dogs and man (131, 132). The threshold dose is about 5 μg/kg, and as doses 1000 times higher administered the same way have no effect upon the blood pressure, heart rate or electrocardiogram, he concludes that the hyperglycemia is not due to leakage of the epinephrine into the general circulation. The hyperglycemic curve is flatter and more prolonged than that from intravenous injections and oddly enough it cannot be eliminated by hypophysectomy, vagotomy, adrenalectomy, or transection of the cervical cord. Norepinephrine and isoproterenol also had this effect intrathecally, as did synephrine, paredrine and, to a lesser extent Neo-Synephrine. Ephedrine, amphetamine and propadrine left the blood sugar unaffected however. We seem to be at a loss to explain the mechanism by which this interesting effect takes place, but more recently discovered hormones from the pancreas such as glucagon, or various hypothalamic factors come at once to mind and deserve investigation.

IV. DISCUSSION, SUMMARY AND CONCLUSIONS

Up to this point, we have considered for the most part *what* epinephrine does to the nervous system. There is some justification now for taking stock of the preceding data and considering *how* or *why* it has these actions, what physiological meaning there may be in it, and what the most pressing needs for future research on this subject are.

As to epinephrine's mode of action upon the brain, it is difficult to account for any of the actions except possibly some of those upon the spinal preparation through alterations in peripheral sensory, motor or autonomic fibers or synapses. Its inhibitory effect on the reticular formation in general and the vasomotor center in particular through the baroreceptor reflexes of the 9th and 10th cranial nerves is well documented and must always be taken into account. The patterns of action of epinephrine upon the brain are so variegated—stimulation of the EEG and wakefulness, lowering the electrical threshold of the motor cortex, and triggering of ovulation on one hand, and inhibition of ADH release, suppression of central thyrotropic hormone control, diminution of cortical evoked potentials, and the production of stupor on the other—that to account for all this simply on the basis of a general increase or decrease of cerebral blood flow would also be highly unsatisfactory, although the significance of local or regional alterations in blood flow is not so easily dismissed and much more difficult to assess. Finally, if epinephrine exerts most of its effects directly upon central nervous tissue, how may one account for this action in the presence of a blood-brain barrier to epinephrine?

It is not necessary to postulate general permeation of the brain by epinephrine for this agent to affect neuronal function. The brain possesses mechanisms for tasting, as it were, the blood flowing through it, measuring its osmolarity, pH and CO_2 tension, and probably its content of glucose and certain hormones as well. A variety of chemical agents trigger vomiting through such an arrangement

(26). It is quite conceivable that receptor mechanisms may be available to epinephrine without its diffusing throughout the brain generally—either through specially intimate relations between the susceptible element and the blood stream [*cf.* the peri- and endocellular capillaries of the supraoptic neurones in many species (232)], through focal absence of the blood-brain barrier altogether, as in the neurohypophysis and area postrema, or through selective variations in the barrier as may obtain with respect to the osmo- and gluco-receptors of the hypothalamus. In this regard, the current work of Axelrod and Weil-Malherbe (8) on the regional permeability of the hypothalamus to epinephrine constitutes an interesting approach to an important question. This problem does not arise with local intracerebral injections, of course, but this method has drawbacks of its own since it can hardly be considered physiologic, and the same objection has been raised to the intraventricular and subarachnoid instillation of these agents.

Marrazzi (160) has postulated a general synaptic inhibitory effect of epinephrine in the central nervous system, explaining outward manifestations of excitation or stimulation as being due to inhibition of inhibitory systems. It is obvious, however, that one could equally well postulate the exact converse. It is becoming increasingly clear from microelectrode studies of the central nervous system that excitation or stimulation, meaning increase in output or activity of a system, is quite a different thing from the increased spike discharge of any given single cell. The action of epinephrine upon cells of the isolated midbrain slab is to increase the firing rate of some, decrease it in others, and leave still others unaffected. Although this tells us that the drug can affect cellular activity directly, it gives us no idea of which is the primary effect or effects, or what the ultimate meaning functionally. Whether epinephrine produces EEG activation by excitation of excitatory cells, inhibition of inhibitory ones, or both, is impossible to decide at the moment.

The fact remains that epinephrine can, in moderate doses, duplicate many of the effects of electrical stimulation of the reticular activating system, in the anatomical distribution of which sympathin (norepinephrine and epinephrine) is known to be present (264, 266). The possibility that adrenergic synaptic transmission takes place within this system (55) or at least within a component of it (212) has been suggested and remains a stimulating possibility. In its favor are the system's relative sensitivity to circulating or injected epinephrine, in areas localized well anatomically to the known sites of central sympathin, and the apparently direct action of epinephrine upon it. Moreover, it is almost certainly no coincidence that many of the most potent and effective central "stimulants"—by which it is meant agents which allay fatigue, postpone sleep, and heighten mood—are adrenergic, *e.g.*, ephedrine, amphetamine and cocaine. Thus they might well act to increase the level of activity of this system which is believed to have so much to do with wakefulness (146). It is possible to relate the central effects of chlorpromazine to its adrenolytic activity, since the syndrome it produces is so closely the reverse that of the above drugs, but here one hesitates for fear of oversimplification, especially when there has been so little study of the specific central effects of other adrenolytic agents.

Whether epinephrine-norepinephrine plays the major role or only a minor one in synaptic transmission in this system, or whether its action is indirect, influencing the effects of another neurohumor such as acetylcholine (39), or working in the manner of a modulapse (II, A, 2) all remain to be settled. In view of the slowness with which epinephrine is believed to be destroyed and the long time it persists in the cerebrospinal fluid, such a synaptic influence may be expected to have certain special properties, including a rather tonic activity and a long latency, with variations being distributed over a longer time base. Properties such as these have been described for the reticular activating system (212, 243), and are clearly characteristic of wakefulness, arousal and many emotional states. It is tempting to attribute to a deficiency of this central neurohumor the defects encountered in extreme fatigue, pathological states such as coma or narcolepsy, or various drug-induced states, some of which have been discussed in this symposium. Even natural sleep may bear some relation to cyclic variations in the production or release of such neurohumors, whether by a pile-up to toxic levels, or by a gradual exhaustion of synaptic stores, the latter appearing the more likely. The therapeutic value of amphetamine and related compounds in such states becomes readily understandable if one postulates that they act by supplanting the deficient neurohumor or, more likely, by increasing the sensitivity of the adrenoceptive elements to what there is. So far, attempts to demonstrate the release from the brain of adrenergic neurohumors during stimulation of the reticular activating system have been unsuccessful (219), possibly due to the failure of such substances to pass in sufficient quantities from the brain or cerebrospinal fluid into the blood stream (II, C).

It is entirely too speculative to relate pathological alterations in mood or wakefulness in the opposite direction, such as hypomania or agitated depressions, to aberrations in such a system, but the writer suggests that the insomnia, irritability and tremor of hyperthyroidism may be due to sensitization of the adrenergic component of the reticular activating system to its own neurohumors. Thyroid hormone does have such an effect upon adrenergic systems, and most or all of the peripheral manifestations of experimental hyperthyroidism have recently been attributed to this sensitizing action, rather than to any direct action of thyroid hormone *per se* (31). Thus the same may hold true for its central manifestations as well.

Because of the marked differences in subjective effects of small doses of epinephrine and norepinephrine, the writer has been forced to postulate central adrenoceptive mechanisms, possibly within the hypothalamus, which unlike the reticular activation system itself are more sensitive to epinephrine than norepinephrine, and which might subserve affective states and mood, rather than the simple maintenance of wakefulness (212). The positive-reinforcing value of intrahypothalamic epinephrine and iproniazid, the marked changes in the electrohypothalamogram from epinephrine (196, 198), the hyperglycemic effect of intrathecal epinephrine, and the possible relation of epinephrine to hypothalamic control of ovulation may all be related, and as previously mentioned the hypothalamus is rich in both neurohumors (266).

The spinal cord seems much less sensitive to epinephrine. Many of the effects of epinephrine upon its activity can be explained by an action on the descending reticulospinal systems, predominantly facilitatory, and by inhibition of these systems through the baroreceptor reflexes. Whether any of these systems might be adrenergic within the cord is problematical, but it is interesting to recall the earlier return of cord reflexes after transection from treatment with ephedrine, the marked reactivity of the cord to epinephrine after denervation hypersensitivity, the selective facilitation of epinephrine upon extensor tone and reflexes, and the fact that chlorpromazine rather selectively alleviates certain types of spasticity characterized by extensor overactivity (91).

The action of epinephrine upon the vasomotor system and the central sympathetics so closely allied functionally with the reticular activating system (22) is highly disputed. Evidence for a central chemoreceptive mechanism responding to epinephrine by a fall in blood pressure has been postulated repeatedly but is still not settled (II, D), and the fact that all these experiments must be performed on deeply anesthetized animals undergoing extensive surgery must be kept in mind. Indirect evidence of the opposite possibility, stimulation of this system by epinephrine, was obtained by the writer in unanesthetized cats after chlorpromazine, and alteration of respiration from epinephrine is a common observation. All these questions must be left unsettled.

There are well documented instances nonetheless in which epinephrine seems to excite systems whose final effect is inhibitory. The prevention of stress or acetylcholine antidiuresis, decrease in rate of TSH release, inhibition of certain spinal cord reflexes, and evidence for stimulation of a reticular inhibitory system have all been reviewed, as have the effects on cortical evoked potentials. Where these effects may be related to adrenergic transmission, there might be a mosaic of different functions under adrenergic control, excitatory and inhibitory. Where they require large doses and take place in central regions poor in sympathin, a purely pharmacologic action is probably more likely.

It remains to explain the curious syndrome of epinephrine stupor. Certain features of this condition, not generally recognized, are becoming clear. Although intraventricular injection is a particularly effective way of producing it, this cannot be attributed to any nonspecific "poisoning" of the tissues lining the third and fourth ventricles, because the same syndrome results from subcutaneous, intramuscular, intravenous and intraarterial injections in a number of species, provided the dose is large enough. Moreover, it would be inadvisable to attribute the effect of epinephrine by these latter routes to a peripheral action, because the syndrome seems the same, whether the drug is administered systemically or intrathecally, and although there is evidence that epinephrine can get into the nervous system, there is none yet that it can get out (see above). The doses required are well above the physiologic range. It requires 20 mg subcutaneously in the cat for example. The required doses intrathecally are less—20 to 80 μg in one series (67)—although it has required somewhat larger doses in our experience (100 to 1000 μg). Epinephrine and norepinephrine seem about equally potent, and a number of other catechols and phenyl derivatives have the same effect,

while still others act in just the opposite fashion, producing excitement in any dose.

Cerebral vasoconstriction and consequent anoxia seem unlikely as causes since intrathecal isoproterenol has the same effect as norepinephrine, since seizures and permanent damage to the nervous system are not seen despite repeated administrations, and since oxygen electrode studies show an increase in cortical oxygen tension rather than a decrease from large doses of epinephrine intravenously (209). While the vomiting and respiratory stimulation come on rather early, the analgesia and stupor have a rather long latency even after intraventricular administration; the latency is not much reduced by raising the dose. Probably because of the rapid clearance of epinephrine from the blood, a single intravenous injection may have no effect unless the dose is dangerously high, but intravenous infusion, by maintaining a supernormal blood level, is very effective and even relatively moderate doses (2.0 μg/kg per min) will produce the syndrome provided it is continued long enough (20 to 30 minutes). Once this is reached, the central effects persist for about 10 minutes after the infusion is stopped even though the blood levels and peripheral effects are known to disappear within 3 to 5 minutes. All this suggests the pile-up within the brain of epinephrine or perhaps some substance derived from it. Adrenochrome and adrenolutin have similar behavioral effects intraventricularly (238), and have been suggested as possible culprits (104). Their formation *in vivo* is disputed, however, and one wonders if this would account for the action of the other related compounds with the same action.

To summarize the possible mechanism of epinephrine stupor-analgesia, the action of epinephrine is probably central, requires large doses, and has a long latency. Vasoconstriction and anoxia of the brain are unlikely. It might be due to a specific effect of certain epinephrine degradation products. If due to the direct action of epinephrine or its congeners, the effect could be pharmacologically nonspecific, because of the large doses required and the ease with which apparently similar syndromes can be produced with other agents (120). On the other hand, a poisoning of normally excitatory adrenergic synapses by these excessive concentrations (1), or through the depressant action of high concentrations of epinephrine upon cholinergic synapses (39) also merits consideration and might have much to teach us.

The possibility of a toxic paralysis of excitatory adrenergic synapses is particularly attractive, since the syndrome is in so many ways the opposite of that produced by small doses of epinephrine. Thus instead of the facilitation of spinal extensor mechanisms, the animal is too weak to stand, although segmental withdrawal reflexes remain active. Instead of the arousal produced by catecholamines or the special alertness and anxiousness seen after epinephrine, the animal is phlegmatic or in an akinetic stupor. Epinephrine in small doses antagonizes the analgesic effect of morphine in man and animals whereas in epinephrine stupor, the behavioral response to pain is reduced or absent even when other functions such as blinking, sneezing and coughing are active and intact. One point needing clarification is the distribution of epinephrine after intrathecal adminstration. It

would be highly desirable to know whether it reaches all portions of the brain or only selected regions, or whether any of it can escape intact into the general circulation. This would complement the studies already in progress on the cerebral distribution of systemically administered epinephrine already referred to.

In conclusion, there is good evidence from study of the effects of epinephrine and its congeners upon central nervous system function that these and related compounds normally play here an important and specific role. At the moment our knowledge of the pattern is only fragmentary, and because of the complexity of the test object our observations are doubtless misleading in some instances. Nonetheless, continued study of the growing list of known neurophysiological mechanisms and the effects of catecholamines upon them should test the validity of the hypothesis and fill in the many gaps. Emphasis must be placed on the study of a variety of such mechanisms, using a wide dose range in different species, all of the modes of administration at our disposal, and if possible without the confusing effects of peripheral action and the masking influence of anesthetics.

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