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BRAIN CENTERS AND POSITIVE REINFORCEMENT

JAMES OLDS

Department of Psychology, The University of Michigan, Ann Arbor

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History

Our present understanding of centers in the brain where positive reinforcement of behavior is produced by direct electric stimulation has its roots in the 1920's and 1930's, with two nearly simultaneous methodological advances. In Switzerland, W.R. Hess (1954) began chronic implantation of electrodes in the brain to study awake, behaving animals by electrically stimulating small brain foci. At about the same time, B.F. Skinner (1938), in this country, introduced the "Skinner box" method for response-reward conditioning.

The next major steps waited until the early 1950's when J.M.R. Delgado (1955), D.O. Hebb (1955), N.E. Miller (1957a), and others began programs aimed at bringing together the chronic implantation methodology and psychological experimentation.

The application of these methods to the problem of positive reinforcement began with an accidental observation made in Hebb's laboratory late in 1953. A chronically implanted rat with an electrode in an olfactory part of the brain was free to move around relatively unimpeded in a field approximately five feet by five feet. The field was bounded by 8-inch wooden sides and a pair of light wires suspended from the ceiling formed a loose leash and a connection to the electric stimulator. The experimenter applied a sine wave stimulus of 60 cycles per second and about 100 microamperes root mean square by pressing a button.

More or less expecting to see some negative reinforcement produced by electric brain stimulation, as had been observed earlier that year by Delgado, Roberts, and Miller (1954), he applied the stimulus each time the animal approached one of the corners.

The surprising observation was that the rat returned to that corner over and over again--much more often than one should have expected either on a negative reinforcement or even on a chance basis. At first interest or curiosity on the part of the rat with respect to the electric stimulus seemed a possible explanation. But a few further tests quickly led to the conviction that here was a genuine positive reinforcement, a <u>brain stimulus with all the characteristics of a primary reward</u>!

There is no need to describe the early tests. Suffice it to say they involved, first, attracting the rat in any chosen direction by stimulating the animal whenever it took a step in the right direction, and, later, provoking normal "T" maze learning and then reversal learning by shocking the brain whenever the animal reached the goal.

While all of these early tests provoked enthusiastic response from experimenter and rats, it was undoubtedly Skinner's method that put the experiments on a quantitative basis. A circuit was arranged so that each response of

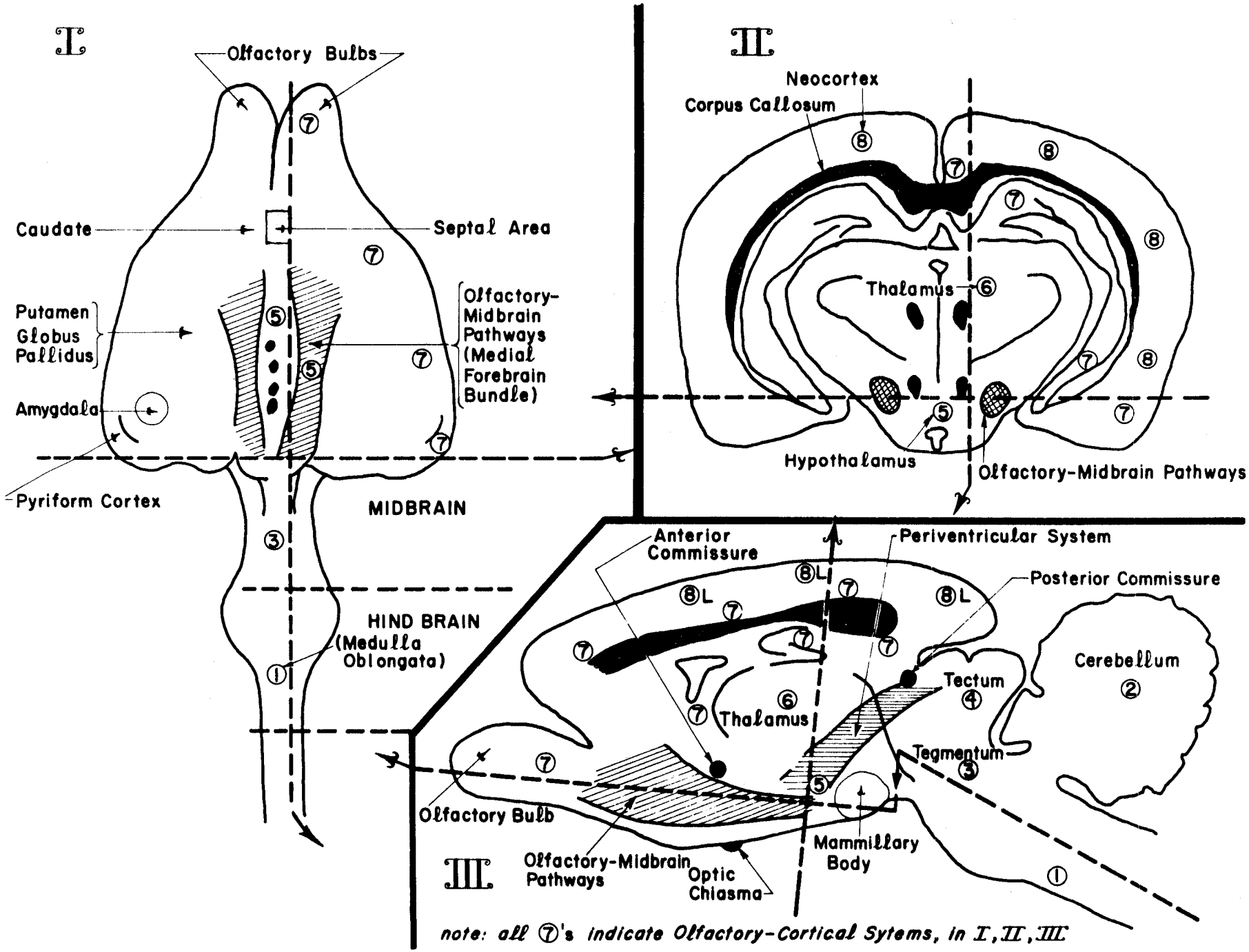

I
Olfactory Bulbs
Caudate
Septal Area
Putamen
Globus
Pallidus
Olfactory-
Midbrain
Pathways
(Medial
Forebrain
Bundle)
Amygdala
Pyriform Cortex
MIDBRAIN
HIND BRAIN
(Medulla
Oblongata)
II
Neocortex
Corpus Callosum
Thalamus
Hypothalamus
Olfactory-Midbrain Pathways
III
Anterior
Commissure
Periventricular System
Posterior Commissure
Cerebellum
Tectum
Thalamus
Tegmentum
Olfactory Bulb
Olfactory-Midbrain
Pathways
Optic
Chiasma
Mammillary
Body
note: all ⑦'s indicate Olfactory-Cortical Sytems, in I, II, III

Fig. 1

the animal produced a brief train of electric stimulation in the part of the brain that was to be studied. With this method, the rate at which the animal stimulated its brain turned out to be a relatively satisfactory measure of the reinforcing properties of the stimulus. We will speak of this behavior as"self-stimulation," and sometimes the brain centers involved will be called "self-stimulation centers".

A series of questions about this positive reinforcement phenomenon have been responsible for the series of further investigations in our laboratory and in others.

Topographic Organization

Possibly the question with the most ramifications is the anatomical one: Where in the brain does this happen? Where do the electrodes have to be placed to produce positive reinforcement?

Brain Structure

The central nervous system of the mammal has the spinal cord at the back and the olfactory bulbs at the front, with the larger part of the brain falling in between. If we start numbering the main parts from the point just in front of spinal cord (see Fig. 1) we find (1) a widening of the pathways of the cord to form the medulla oblongata or hindbrain whose integrity is essential to basic physiological processes. (2) Perched above the boundary-line between this hindbrain and the next major subdivision is the cerebellum with its still little known sensory-motor functions. Beyond the hindbrain, the next major subdivision is the midbrain. (3) Its lower part, the tegmentum, is most famous for the "reticular activating system" which has recently come into vogue as the "waking" center of the brain. (4) The upper part of the midbrain, the tectum, is devoted mainly to vision and audition.

Figure 1. Three views of the rat brain. I. As seen from above with top of head and top of brain cut away. II. As seen from in front with much of the front end cut away. III. As seen from the side with one side mostly cut away. The two arrow-tipped dotted lines on each picture show how the brain would be cut to get the other two pictures. Dotted lines on picture I are also used to mark the extent of the hindbrain and midbrain. Because of left-right symmetry, everything which appears on one side of pictures I and II occurs also on the other side even though it is unmarked. For further discussion, see text.

In front of the midbrain is the forebrain whose parts are enumerated below. Not too long ago, as phylogenetic history goes, the whole forebrain was nothing but the olfactory bulbs, which were connected loosely to the midbrain by two long tubes which make up the hypothalamus. Above these tubes there developed the olfactory lobes (rhinencephalon) which are now known as the palecortex, and then the thalamus and the neocortex. The forebrain includes, therefore, (5) the hypothalamus and (6) the thalamus; the two together make up the diencephalon or "in between" brain. In front of and spreading back over these, the forebrain also includes (7) the paleocortex and (8) the neocortex; these two together with certain boundary regions and with the olfactory bulb itself make up the elencephalon.

On the boundary between telencephalon and diencephalon are structures which form bridges between diencephalon and the various parts of the cortex. Using the analogy of a clock, with the area just in front of the thalamus at 12 o'clock, we find (a) septal area at 12 o'clock (see Panel No. 1 of Fig. 1), (b) caudate at 1 o'clock, (c) putamen and globus pallidus at 2 o'clock, and (d) amygdala at 3 and 4 o'clock. The parts of the paleocortex are the subcallossal cortex, the pyriform cortex, the cingulate cortex, and the hippocampal cortex which has a peculiar position, stuffed in between the thalamus and the cortex in spaces not filled by the bridges.

The backward projecting tubes from the olfactory bulb make up the lateral part of the hypothalamus surrounding the hypothalamic nuclei which have settled in the middle of this olfacto-tegmental stream. The stream itself is spoken of as the medial forebrain bundle (MFB); it arches across the midline just above the most posterior of the hypothalamic nuclei (i.e., just above the mammillary body).

Field and Focus

Positive reinforcement produced by electric stimulation of the brain was originally discovered in rats with electrodes in a boundary system between the olfactory bulbs and the older olfactory parts of the cortex (Olds and Milner,1954). It was first thought to be mainly related to the olfactory cortex or rhinencephalon. Positive reinforcement could be produced by stimulating some parts of almost all rhinencephalic structures. In rats it became clear that more than half of the electrodes placed at random in the olfactory cortex would yield positive reinforcement when stimulated electrically. Later studies showed that the "focus" of the phenomenon, if maximum responding for a minimum of stumulation could be taken to indicate a focus, was not in the olfactory cortex but in other olfactory projections directed toward the spinal cord through the hypothalamus and midbrain (Olds, 1956a; Olds and Olds, 1962; Olds et al., 1960). In fact, there is a pair of long tubes extending from the olfactory bulbs and olfactory cortex which pass along the two outer edges of the hypothalamus and into similar areas, i.e., the lower and lateral areas, of the midbrain. While much of the area between and surrounding these tubes seems to yield positive reinforcement when electric stimulation of the brain is applied, the tubes themselves seem to comprise the focus of the phenomenon, if maximum effect from minimum stimulation is used as the criterion. We will speak of this "focus" as (a) the olfactory-midbrain pathway, or (b) the medial forebrain bundle (MFB), or (c) the lateral hypothalamic area--these three labels being roughly equivalent.

We will speak of the rhinencephalic structures and of other areas which

yield milder effects as a surrounding "field", which is considered to be more orless loosely linked to the "focus" of reinforcement. Some interchangeable labels used to designate this milder reinforcement "field" are (a) the olfactory-cortical areas or pathways, (b) the rhinencephalon, (c) the paleocortical system, and (d) the limbic system. The olfactory-midbrain pathways, which make up the focus, envelop, on their route from cortical to midbrain centers, an important system of nuclei in the lower middle part of the brain. At this point in their course, the olfactory-midbrain pathways, together with the surrounded nuclei, are known as the hypothalamus because this area lies below the thalamus, which makes up the upper middle part of the brain. All parts of the hypothalamus yield positive reinforcement, but only the lateral part, i.e., the pathways, makes up the focus. Thus the midline nuclei of the hypothalamus can be considered to be part of the "field".

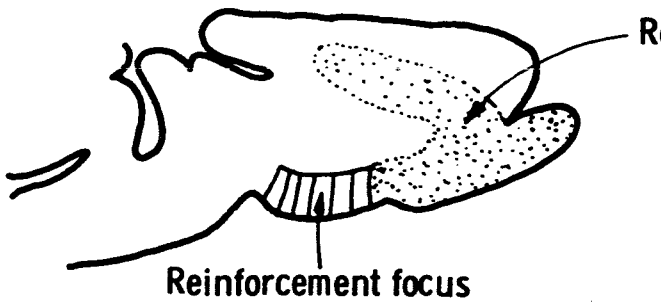
A number of differences between the positive reinforcement produced by hypothalamic "focus" stimulation and that produced by rhinencephalic "field" stimulation have been observed. First, in experiments where each response was followed by one "stimulus-reward", response rates were far higher with hypothalamic stimulation. Animals would press a lever 10,000 times an hour to stimulate the lateral hypothalamus, but only about 500 times an hour, under the same conditions, to stimulate the olfactory cortex areas (Olds, 1958f). Second, appetite for stimulation at the focus often seemed relatively insatiable, whereas a definite satiation point was usually reached in experiments with field stimulation. Animals stimulated themselves hour after hour in the lateral tube, maintaining a rate of several thousand responses per hour and stopping only when a state of physical exhaustion appeared (Olds, 1958c). Third, the reward produced by focus stimulation seemed to be accompanied by a heightened general activity level (Roberts, 1958b), whereas the reward produced by olfactory cortex stimulation often seemed to be accompanied by more or less inhibition of general activity (Olds, 1956b). Fourth, although there were some apparent pain- or anxiety-relieving effects of the rewarding stimulus near the olfactory cortex (Brady and Conrad, 1960b), there were places in the hypothalamus where the reward stimulus did not have these effects (Olds and Olds, 1962).

In other mammals the picture was similar. Brady (1956; 1957; 1961), Nielson et al. (1958), Sidman et al. (1955), Brown and Cohen (1959), Roberts (1958b), Wilkenson (1963), and Justenesen et al. (1963) have studied cats. Electodes in the olfactory-midbrain focus yielded positive reinforcement with great regularity. Bursten and Delgado (1958), Brady (1961), Lilly(1957),* Brodie and his group (Brodie et al., 1960a, 1960b), and Porter et al. (1959) have studied monkeys. Here also, electrodes in the olfactory-midbrain system yielded positive reinforcement of great intensity. Olfactory-cortical structures also yielded positive reinforcement in varying degrees on electrical stimulation.

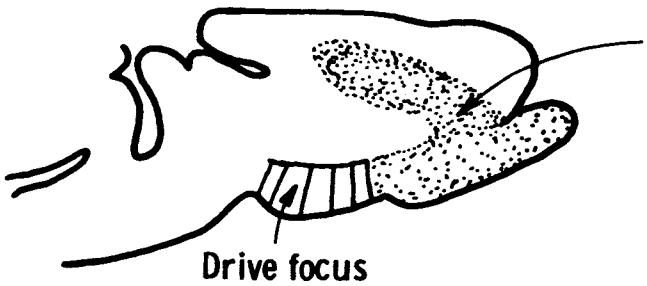
Lilly (1962) reported a study of the bottle-nose dolphin. Some electrodes in the very large brain of this mammal yielded positive reinforcement; however, the precise location of the electrodes was impossible to determine from the report.

Higgins et al. (1956), Delgado and Hamlin (1960), Heath (1960), Sem-Jacobsen and Torkildsen (1960), and Bishop et al. (1963) have reported on humans who had chronic electrodes implanted in the brain for therapeutic

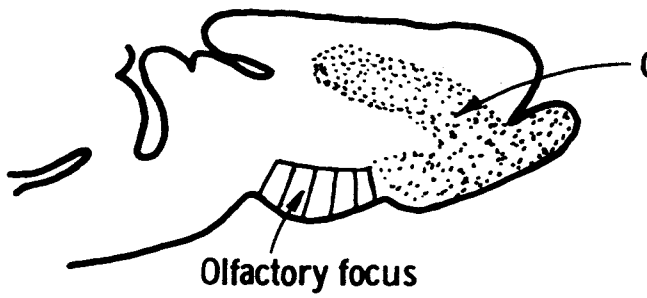
*Much the same data are found in: Lilly (1958a, 1958b, 1959a, 1959b, 1959c, 1960a, 1960b.)



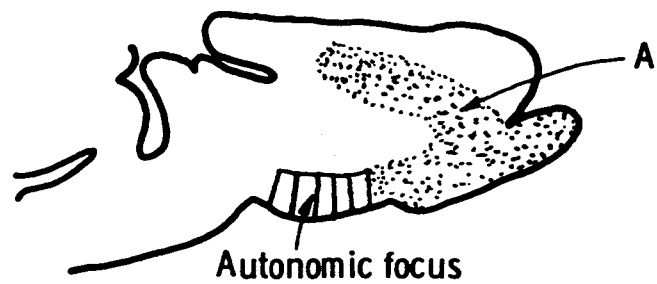
1. Continuity of field and focus
2. Size of focus + field = 1/3 of brain



3. Overlap with drive system



4. Overlap with olfactory-chemorecepor system



5. Overlap with autonomic system

Fig. 2

purposes. Subjective reports have not been extensive. Electrodes believed to be in the olfactory-midbrain pathways have produced "extreme euphoria", while electrodes in the olfactory-cortical field have inhibited pain, and produced feelings of "well being". Several patients with olfactory-cortical electordes in frontal areas have expressed desires to "marry the investigator" (Delgado and Hamlin, 1960).

The functional implications of the anatomical findings were more important than the nomenclature, and I will emphasize them here (see Fig. 2) and in the next three sections.

Figure 2. Pictures to emphasize the overlap of brain areas involved in reinforecement, drive, olfaction, and autonomic function.

In the first place, the system of regions where electric stimulation caused positive reinforcement was continuous (Olds et al., 1960). The olfactory pathways directed from the bulb toward the midbrain were continuous with the olfactory pathways directed from the bulb toward the olfactory cortex. It appeared, therefore, that one topographically continuous system of brain structures made up the focus and the field of these regions. This seemed to suggest a common mechanism. In the second place, it was an extensive region making up almost one third of the brain in the rat, and while it was a smaller portion of the brain in the higher mammals, still, a substantial portion of the brain was involved even in the macaque and the human. In the third place, three other functions were regularly ascribed to this whole series of sturctures: (i) olfactory reception, (ii) control of basic drives, and (iii) regulation of autonomic function. I shall devote a section to each of these.

Olfactory Relations

The olfactory or chemoreceiptive function of these brain regions was indicated by the appplied names, rhinencephalon and olfactory brain (Papez, 1937; Pribram and Kruger, 1954). The names were applied because the structures involved all have fiber connections with the olfactory bulb or with related structures; and also they seem to be derived phylogenetically from olfactory structures. For a while, it was in fashion to say tha these structures made up an emotional brain once thought to be mainly olfactory. I argue that these structures make up an olfactory and chemoreceptor brain even now, but that chemoreception is directed not only toward smelling the environment, but also toward the sugars and hormones in the blood, which have so much to do with controlling high drive behaviors. It appears to me wise, therefore, to emphasize the phylogenetic and functional connection of these structures to the olfactory bulb, and the widespread discovery of chemoreceptive functions within these structures themselves (Anand et al., 1961; 1962; Harris et al., 1958).

One might even go so far as to suggest a rigorous phylogenetic link between olfactory mechanisms and positively reinforced behavior. It is not impossible that aversive reactions were the only ones deriving from the irritability inherent in protoplasm, and that appetitive reactions were a later phylogenetic development awaiting the evolution of an olfactory apparatus. A specialized chemosensitive receptor occurs in coelenterates and platyhelminthes; in both it serves to guide behavior in pursuit of food. In insects the chemoreceptor has come to subserve another appetite as well, indicated best, perhaps, by the gypsy moth, which will home over two miles on the odor of a gypsy female (Jahn and Wulff, 1950).

The forebrain, as soon as it appeared in the phylogenetic series was also linked to olfaction. It appeared first in early vertebrates where, in the shark for example, the brain seemed but a loose conjunction of the midbrain and a long, forward protuberance, the olfactory bulb and olfactory lobe. Here, again, there was an appetitive function linked to this olfactory apparatus, and its form suggested that there is much in common between our notions of appetitive reaction and "operant" behavior; amputation of the forebrain caused fish to lose "initiative," that is, "the ability to react to stimuli in a specific, nonreflex manner" (Prosser, 1952).

The experiments of the present review might be taken to indicate that the appetitive behavior, which was from the start sedded to the chemoreceptor system, is still so bound, although the direction of ehcmosensitivity has shifted away from its original external orientation and toward the blood and cerebrospinal fluid of the milieu interne. In the course of this change, what started as appetitive behavior has evolved into a whole system of operant or voluntary mechanisms, and the forebrain, which started as a small olfactory appendage, has developed to a point where it comprises almost the whole brain.

Drive Relations

The hypothalamus and rhinencephalon have long been known to house a series of drive centers, i.e., a series of centers related to eating, drinking, temperature regulation, sexual behavior, and so forth. Because of the ubiquity of drive control functions within this system. MacLean (1949) labelled it the "visceral brain." Without even attempting to be complete, I can mention the work of Kluver and Bucy (1939), Anand and Brobeck (1951a) 1951b, 1952), and Stellar and Teitelbaum (Stellar, 1954; Teitelbaum, 1955; Teitelbaum and Stellar, 1954) in which olfactory-midbrain and olfactory-cortical systems were shown to have drive relevance because lesions within these systems regularly cause disorganization of drive behaviors. Many cases of feeding "hyperphagia" and "aphagia: and aberrations in sexual and aversive behavior were observed to ensue as a consequence of experimental lesions placed in these areas. An interesting difference between the hypothalamic "focus: and the rhinencephalic "field" was suggested by these lesion studies.

Lesions at the focus appeared to upset control of behavior by the internal dirve state; thus animals with hypothalamic lesions either failed to eat when they were deprived, or failed to stop eating when they were sated. In either case, there was excessive control of eating behavior by stimulus factors, that is, whether eating was excessive or reduced, animals with

hypothalamic lesions had more than the ordinary tendency to approach appetizing foods or to avoid unappetizing foods (Teitelbaum, 1955; Teitelbaum and Stellar, 1954) Lesions in the rhinencephalic field, on the other hand, appeared to upset the control of behavior by various reinforcing stimulus objects The animals with lesions in the olfactory cortex could not discriminate edible from inedible objects until the objects were in their mouths; they responded sexually not only to appropriate sexual partners but even to inanimate objects; and they did not appear to respond in the usual way to objects which had formerly posed a threat (Kluver and Bucy, 1939). Thus, one might conclude that the field mediates control of behavior by reinforcing stimulus factors, and that the focus is either a more basic behavioral control center or a mediator for more visceral and hormonal factors.

Not only has positive reinforcement been regularly provoked by stimulating approximately the same areas as those previously implicated in studies of basic drives, but at many brain points, the behavior leading to stimulation was also augmented or diminished by manipulation of at least one of the basic drives Furthermore, with stimulating probes at different brain points, different drives were effective.

When electrodes were placed in the so-called "feeding center of the lateral hypothalamus," which is a part of the olfactory-midbrain pathway, self-stimulation at high rates was provoked; food deprivation usually caused increments in the self-stimulation response rates in rats (Herberg, 1963a; Hoebel and Teitelbaum, 1962; Margules and Olds, 1961) and cats (Wilkinson and Peele, 1962). Food deprivation caused similar increments when electrodes were placed in certain parts of the olfactory-cortical pathways in rats (Brady et al., 1957; Hodos and Valenstein, 1960; Olds, 1958b), and when electrodes were placed in slightly different parts of the same pathways in cats (Brady et al., 1957; Nielson et al., 1958). With electrodes in some of these olfactory-cortical pathways, the effect of thirst appeared to be similar to that of hunger (Brady et al., 1957), but this was not clearly established as a separate effect. Castration and androgen-replacement therapy have been shown to control self-stimulation rates with electrodes in other parts of the olfactory-cortical and olfactory-midbrain pathways (Herberg, 1963a; Olds, 1958b, 1958e). With some electrodes in the most posterior part of the olfactory-midbrain system, self-stimulation behaviors seemed to be augmented by "fear" produced by a loud noise or mild shock (Deutsch and Howarth, 1962).

The hunger-related rates produced by stimulating hunger-sensitive parts of the olfactory-cortical pathways were not susceptible to augmentation by raising estrogen levels in female rats (Hodos and Valenstein, 1960). A similar dissociation of hunger and androgen effects was reported for male rats (Herberg, 1963a; Newman, 1961; Olds, 1958b). In general, it appeared that placements yielding self-stimulation rates which were susceptible to positive control by the hunger drive were different from placements whose rates were susceptible to positive control by sex hormones (Herberg, 1963a; Olds, 1958b)

The problem of drive in relation to self-stimulation is far from solved. The first major area of difficulty is posed by the extremely small differences often observed when drives were effective in modifying self-stimulation rates with electrodes in the olfactory-midbrain pathway. Some of these differences were so small that they might have been made by changes in the general activ-

ity level (cf. Valenstein, in press, 1964). That general activity did not account for all such differences was suggested when a given "drive" modified the incentive value of one brain stimulus but not another in the same animal (Wilkinson and Peele, 1962). In any event, the differences, when hypothalamic electrodes were used, usually appeared to be smaller than would have been expected with a normal food incentive (Herberg, 1963a; Olds, 1958b). I believe that this difficulty may eventually be attributed to one or more of the following factors: (1) the size of the suprathreshold self-stimulation field is usually so large that it invades more than one drive-reward field; (2) the stimulus itself, invading an area which receives both "drive" and "reward" projections, may have two simultaneous effects, reinforcing antecedent behaviors on the one hand and inducing the correlated drive on the other (cf. Hoebel and Teitelbaum, 1962; Howarth and Deutsch, 1962; Margules and Olds, 1961; Miller, 1957a); and (3) with many "incentive-motivated" behaviors, it has been observed that when the reward was sufficiently "attractive" no antecedent drive created by deprivation was necessary to motivate behavior.

A second difficulty poses itself mainly as an area of insufficient evidence. This is the area of drive effects on self-stimulation with electrodes in olfactory-cortical pathways. In some of these cases, as Valenstein (in press, 1964) has pointed out, experiments have been made with brain sites or stimulus levels which yielded questionalbe self-stimulation rates, e.g., the work of Justenesen et al. (1963). In these cases, because self-stimulation rates were low in the first place, very large changes could be produced by drive manipulations without allaying the suspicion that general activity, rather than changes specifically related to the incentive value of the lectric stimulation, were involved. In other similar tests, however, there were substantial self-stimulation rates and very striking all-or-none differences were made by manipulation of drives (Olds, 1958e). Very few of these cases, however, have been reported to date and therefore a question remains whether they occurred by accident or could be reproduced at will. In some experiments with cats, similar all-or-none differences in substantial rates were reported with electrodes in the olfactory-midbrain pathway (Wilkinson and Peele, 1962). The hope exists, therefore, that olfactory-cortical and olfactory-midbrain systems may eventually be categorically analyzed into various drive-reward subsystems. The olfactory-cortical pathways may yield to more research along present lines; even the olfactory-midbrain system may be so analyzed if special techniques (Herberg, 1963a) or larger animals (Wilkinson and Peele, 1962) are used.

In other experiments, it was demonstrated that in addition to positive reinforcement, the same brain probes often yielded the consummatory response appropriate to one of the basic drives if the stimulus was delivered by the experimenter, and the response opportunity existed. In these experiments, electrodes were first tested for elicitation of consummatory or other drive-related responses and then for rewarding effects.

It has long been known that electrodes in lateral hypothalamic "feeding centers" elicited eating responses, and that lesions in these areas caused more or less complete cessation of eating (Anand and Brobeck, 1951a; 1951b; 1952; Delgado and Anand, 1953; Hess, 1954; Morgane, 1961; Teitelbaum and Stellar, 1954). With increasingly detailed mapping of self-stimulation (Olds et al., 1960), it became clear that this same lateral hypothalamic sector was one of several regions of the olfactory-midbrain pathway yielding

maximal positive reinforcement with electric stimulation (Wendt and Olds, 1957). It was shown, in fact (Margules and Olds, 1961, Miller, 1961b) that many of the same electrodes which elicited eating responses also caused positive reinforcement of operant behavior, and that the threshold stimulus level was sometimes the same for the two kinds of effect. A study by Hoebel and Teitelbaum (1962) also showed that stimulus-controlled eating and hunger-related self-stimulation could be obtained by stimulation of the same electrodes in the "lateral hypothalamic feeding center." Near the "feeding center," there is another midhypothalamic region known as the "satiety center" (cf. Brobeck, 1946; Miller et al., 1950) because lesions in it have caused animals to eat insatiably until great obesity appeared. Hoebel and Teitelbaum (1962) showed that stimulation of the satiety center caused elimination of both eating and self-stimulation responses caused by concomitant stimulation in the feeding center. These findings seemed to indicate a structural and functional overlap of a center responsible for lowering the threshold of eating reflexes and a center responsible for hunger-related positive reinforcement.

With respect to thirst, a region in the posterior lateral hypothalamus of the goat yielded voracious drinking upon electric stimulation (Anderson et al., 1958). A homologous point in the rat yielded very intense positive reinforcement (Olds and Olds, 1963).

In the studies of hunger (Grastyan, et al., 1956; Miller, 1957a) and thirst (Anderson, 1953), stimulation of the rewarding lateral hypothalamic "drive" center not only caused consummatory behavior when the goal was presented but also specific, learned, goal-directed instrumental responses when food or water were absent.

Quite recently (Herberg, 1963a), a similar relationship between some of the sexual centers and self-stimulation has been demonstrated. A great deal of work (Brookhart and Dey, 1941; Dempsey and Rioch, 1939; Dey et al., 1940; Fisher, 1956; MacLean, 1958; MacLean and Ploog, 1960; MacLean et al., 1959; 1960; 1961; Sawyer, 1960) has implicated a variety of nervous system structures in various sexual phenomena. Included were parts of the olfactory-cortical system and parts of the olfactory-midbrain system. All of these areas have also been implicated by positive reinforcement tests (Olds,1956; Olds et al., 1960; Olds and Olds, 1963). In early tests with rats (Olds, 1958b), a part of the olfactory-midbrain pathway (called the supramammillary region) appeared to yield androgen-related positive reinforcement. However, only one case was offered in evidence. Later, the work of MacLean and his colleagues (MacLean, 1958; MacLean and Ploog, 1960; MacLean et al., 1959; 1960; 1961) showed that in monkeys a homologous area seemed to be involved in stimulus-provoked sexual responses. Very recently, in a careful study with sufficient numbers of rats, Herberg (1963a) showed (1) that this was an area producing rapid self-stimulationg, (2) that self-stimulation in this region was regularly accompanied by semina discharges without penile erection, (3) that stimulation in this region by the experimenter produced similary sexual response, and (4) that the self-stimulation behavior provoked with electrodes in this region was quite likely augmented by high androgen levels and depressed by hunger. Herberg speculated that a lower, medial quadrant of the olfactory-midbrain pathway was devoted to sexual behavior, some other quandrant of the same pathway being devoted to eating behavior. His data appeared consistent with earlier data (Olds, 1958b) in suggesting a possible negative interaction between the sexual and eating systems.

As a result of these studies it appears increasingly likely that at a brain point where electric stimulation lowers the threshold of the instrumental and consummatory responses appropriate to a given drive, stimulation will also yield rewarding effects the intensity of which will vary as a function of the same drive. One is tempted to suppose that several drive-reward systems exist, and that, in each case, the threshold of the system varies with appropriate hormonal or deprivational conditions. Moderate activity in the system would lower the thresholds of related instrumental and consummatory responses, and the strong activation of the system would function as positive reinforcement of behavior.

Because stimulation applied to many points in the "visceral brain" induces positive reinforcement as well as some instrumental or consummatory "drive" response, we are forced to imagine a closely interwoven pair of systems mediating the control of behavior under conditions of deprivation on the one hand and conditions of consummation on the other. There even seems to be a third member of this group which controls behavior under the condition of satiety, following excessive consummation. Thus, as indicated above, in the hypothalamus, (1) a lateral area is known as the "feeding center" because with lesions in the area animals must be forced to eat and with stimulation, "hunger" appears to be evoked; (2) electric stimulation in this feeding center not only evokes "hunger drive" but apparently causes, at the same time, some positive reinforcement of behavior; and (3) a nearby medial area is known as the "satiety center" because with lesions in the area the animals do not become sated normally but will eat until they become excessively obese.

Autonomic Relations

The olfactory-cortical and olfactory-midbrain pathways comprise, among other things, the system of structures which has been shown to hold the higher control centers of autonomic function. The sympathetic and parasympathetic centers were discovered by W.R. Hess (1954) in the earliest work utilizing chronically implanted depth probes.

It is interesting to consider that three heavily overlapped systems, i.e., (1) the chemoreceptor, olfactory mechanism; (2) the system of drive regulatory mechanisms; and (3) the higher control centers of autonomic function, should now turn out to be overlapped again by a new common denominator, namely, the fact that behavior controlled by reinforcement can be elicited by stimulating almost all of these structures. In order to emphasize again the extreme ubiquity of reinforcement sites within this system of structures, I will say this: I doubt if there are any points in the olfactory-visceral-autonomic brain which do not yield positive or negative reinforcement of behavior. The vast majority of points yield positive reinforcement or a mixed positive and negative effect.

Autonomic Responses

Hess (1954), who first studied the autonomic consequences of electrical stimulation, divided hypothalamic responses into two types: "ergotropic" and "trophotropic." Ergotropic responses were related to the sympathetic nervous system but included some somatic expressions, i.e., "voluntary" be-

haviors. These responses were considered to enable muscular effort such as in defense, attack, or flight. Among the responses were pupillary dilatation, rise in blood pressure, increase in pulse rate, activation of respiration, increase in motor excitability, and general excitement of the animal.

In contrast, trophotropic activities of a parasympathetic type released tension by diminishing the capacity of the organism to produce physical effort, and provided rest and restitution after strain. Such responses included slowing of respiration, drop in blood pressure, micturation and defecation, salivation, pupillary contraction, and loss of skeletal muscular tone.

By electric stimulation in chronically-implanted cats, Hess produced ergotropic responses in a large region in and around the midbrain end of the olfactory-midbrain pathways. Thus most of the posterior hypothalamus was involved. All ergotropic responses tended to go together so that a point which gave one of these effects ordinarily produced all of them.

The points where stimulation produced trophotropic or parasympathetic effects were found to be dispersed over the olfactory-midbrain system. Thus most of the anterior hypothalamus was involved. Trophotropic effects did not show as much tendency to go together as was seen in the ergotropic responses. Micturation, defecation, slowing of respiration, and decline in blood pressure were observed on stimulation of most regions of anterior hypothalamus and of the neighboring olfactory field. The lateral part of the anterior hypothalamic region also produced the other trophotropic responses, i.e., salivation, pupillary constriction, and loss of muscular tone. This loss of muscular tone, called "adynamia" by Hess, involved the animal's sinking down like an inert mass, without any of the normal adjustments involved in lying down. The eyes stayed open; the state was quite different from "sleep", which Hess seemed to produce by stimulating the region of the thalamic intralaminar nuclei. Finally, an area which produced only pupillary contraction and arrest of breathing was also found in and above an anterior region of the hypothalamus. The only one of the trophotropic effects found over the whole region seemed to be arrest of breathing.

Some tendency of parasympathetic-like response to be found in areas associated with positive reinforcement, and of sympathetic-like responses to be found in areas associated with negative reinforcement was at first suggested (Olds, 1958a); however, the correlation was not confirmed. That there should be mixed autonomic responses from a drive-reward system is reasonable, considering the widely variable nature of the instrumental-and-then-consummatory behavior series involved.

Autonomic responses of an even more mixed nature were yielded by stimulation of the rhinencephalic field (Gastaut et al., 1952; Gloor, 1956; Kaada, 1951; Kaada et al., 1954). Moreover, quite often two mutually opposed effects were achieved from a single point, depending on differences in anesthesia, stimulus parameters, or other factors. For example, respiration was inhibited or excited, depending on anesthesia levels with stimulation in one place (Hess et al., 1952). Blood pressure was raised or lowered by stimulation of another point, and the nature of the effect varied with changes of anesthesia or stimulus parameters. Activity of the stomach was started or stopped by stimulation of a third point; in this case, a reversal of background stomach activity was the rule (Kaada et al., 1954).

Similar reversals appeared when excitation and inhibition of somatic "voluntary" movements were studied under stimulation in the same areas. In unanesthetized or lightly anesthetized animals, stimulation of rhinenceophalic areas seemed to inhibit or arrest spontaneous movement. In these same animals, after administration of anesthesia, facilitation of reflex or cortically induced movement was often observed (Kaada et al., 1954).

It is perhaps relevant that both positive and negative behavioral mechanisms of reinforcement involve excitation and inhibition. The animal is often provoked to activity by "anticipation" of reward caused by a conditioned stimulus, and yet the same animal may be pacified by the application of the reward stimulus itself. Conversely, with a punishing stimulus, the animal may be inhibited by aniticipation of it, yet be provoked into intense activity by its application. Thus it is not surprising to find reversible excitations and inhibitions of somatic movement derived from electrical stimulation applied to areas that may form physiological substrates for these mechanisms. The challenge is to specify the conditions of the two phenomena in the hope that this might further the understanding of the actual mechanisms of reinforcement.

There have been three studies in which the same brain stimuli were tested for both reinforcing effects on skeletal behavior and autonomic effects on heart rate. In the first of these, Malmo (1961) reported that stimulation in olfactory-cortical pathways, which produced mild positive reinforcement, also produced cardiac slowing. More recent studies by Meyers et al. (1963), Perez-Cruet et al. (1963) indicated clearly that the long run effect of stimulation in some parts of the olfactory-cortical field is a slowing of heart rate, although there is often a brief rise immediately after stimulation (Meyers et al., 1963). However, these same two studes indicated that the effect of stimulation in the hypothalamic focus is quite different. On stimulation there is a rise in heart rate which may or may not fall back to the prestimulation level. Thus on olfactory-midbrain stimulation, there is often an overall, as well as a momentary, increase in the heart rate, but apparently never a slowing.

Dependent Variables

In numerous studies, the effects of brain-stimulus reinforcement have been compared with the effects of ordinary reinforcement under widely varying circumstances. These comparisons were undertaken as part of a general program aimed at discovering whether the stimulated neural tissues might form part of a substrate of natural positive reinforcement phenomena. It is important to remember in considering these comparisons that the answers could never be unique because brain-stimulus reinforcement differs for each locus of the stimulating probes and for each intensity of stimulation.

Movement from Place to Place

In the simplest demonstration of the production of positive reinforcement by electric stimulation, the stimulus was applied whenever the animal walked into a particular subdivision of a test chamber. In these experiments,

the ESB was considered to cause positive reinforcement if the animal returned with a greater-than-chance frequency to the place where it received the stimulus (Bursten and Delgado, 1958; Olds, 1955a; Olds, 1955b). In one series of experiments (Olds, 1956b), a runway connected a start compartment with a goal box; hungry rats traversed it faster for a stimulus reward than for a food reward. In one of these experiments, animals first performed in a runway, after which the start compartment and goal box were connected by a maze instead of a runway. Hungry rats showed trial-to-trial improvement in both speed and accuracy, learning the maze somewhat faster for a food reward but traversing it faster for ESB reward. Day-to-day improvement was demonstrated even on the first trial of each day, indicating that approach behavior occurred without a prestimulus. In these experiments, electrodes were implanted in olfactory-cortical areas; later experiments showed that some rats with hypothalamic electrodes learned even faster (Olds et al., 1960).

In other tests, however, many stimulation points which caused quite satisfactory self-stimulation behavior did not similarly sustain runway or maze performances (Newman, 1961; Spear, 1962). A partial explanation was given by experiments which showed that for some electrodes a prior "bout" of "priming" stimulation was necessary before the brain stimulus would serve as a satisfactory incentive for runway performance (Wetzerl, 1963); for stimulation via other positive electrodes, animals ran well without priming. Histological data were not presented, but it appeared that small differences in anatomical location of the electrodes might account for the observed differences. The data were not compatible with the view that prior stimulation served to activate the animal generally or to motivate performance because: (a) animals did not run faster to food after the priming, and (b) the brain stimulation often appeared to be aversive before the priming. The author suggested that the priming bout served to attenuate some initial aversive characteristics of the brain stimulation which might initially have ambivalent effects, but, after some preliminary stimulation, have more purely positive effects. One might think of a bather's response to water.

Other data indicated that for ESB reward via some electrodes there was an overnight decrement in maze performance as contrasted with an overnight improvement for food reward (Olds, 1956b). The explanation, in terms of an initial ambivalence, might be applicable, but these data also permit a simpler explanation. In the study in question, each day's first trial was better than the previous day's first trial, indicating (a) day to day improvement, (b) overnight retention, and (c) that priming was unnecessary. However, the last run of one day was always better than the first run of the next day; this might indicate only a warm-up effect. That a similar warm-up effect did not appear with food reward could be attributed to the fact that in the case of food it was counteracted by a strong and readily apparent satiation tendency in the course of a day's trials.

Self-Stimulation

The most widely used method of measuring reinforcement is, of course, Skinner's operant method. The application of the term "self-stimulation" to ESB reward phenomena was popularized by Brady (Brady, 1958a; 1960a); the term refers to the response made by the animal to trigger an ESB reward. In experiments using a Skinner box for which the operant level was in the 15-50

rph (responses per hour) range, the acquisition scores of rats often ranged higher than 8000 rph when olfactory-midbrain stimulation was used as reinforcement (Olds et al., 1960). Rates of 300-1000 rph were the rule with electrodes in olfactory-cortical areas (Olds et al., 1960; Olds and Olds, 1963; Wurtz and Olds, 1963). In self-stimulation experiments with monkeys, rates of 17 responses per second have been reported for brief intervals (Lilly, 1958a).

Extinction and Ratios

In extinction tests, response rates often have dropped off very rapidly after the brain stimulus reinforcement was withdrawn, so rapidly that this was thought by some to indicate a major difference between brain stimulus reinforcement and reinforcement with more ordinary stimuli (Deutsch, 1963a; Deutsch and Howarth, 1963; Olds and Milner, 1954; Seward et al., 1959; Sidman et al., 1955). The argument was that extinction occurred more rapidly than would be expected, considering the very high response rates during acquisition (Olds and Milner, 1954; Seward et al., 1959). And by the same token, animals pursuing ESB did not sustain very high response ratios, i.e., they would make eight but not 50 lever responses for one brain-stimulus reward (Sidman et al., 1955).

Whatever the reason for the rapid extinction and low response rations observed in many cases, it is clear that esceptions have also been observed. With stimulation in the medial forebrain bundle in monkeys (Brodie et al., 1960a), a very large response output during extinction and ratios higher than 100 responses for one ESB were observed. Another study indicated that when stimulation was in posterior parts of the olfactory-midbrain pathways, reversal learning was slower if ESB rather than food was used as reward (Kling and Matsumiya, 1962). The authors of the latter work considered the slow reversal learning to indicate that there was nothing inherently impermanent about responses conditioned with ESB reinforcement, and that in certain test they might be even more persistent than food reinforced responses.

Exceptions to the contrary notwithstanding, it appeared that persisting response patterns were easier to come by with food than with ESB rewards. The question is, Why? Howarth and Deutsch (1962) suggested that the ESB was simultaneously a drive inducer and a rewarding stimulus because it affected two proximal or interdigitated pathways. They believed that the animal stopped responding rapidly not because true extinction had occurred but rather because the ESB induced drive dissipated rapidly; they seemed to suggest that there was no incentive value in the ESB reward in the absence of the ESB induced drive. In support of this view, they presented a Skinner box experiment in which a removable lever was used. The animals that showed little enough responding in the extinction anyway showed even less after the lever was removed for 10 seconds and then reinserted. Responding after reinsertion was so much less that the authors concluded that extinction was a function of time rather than of unrewarded responses (as it is considered to be in food experiment).

In another experiment making the same point, Deutsch and Howarth (1963) showed that thirsty, self-stimulating rats often preferred ESB to water if offered a choice immediately after ESB. The probability of a choice of ESB over water, however, declined as a function of thirst and as a function of the interposed interval between the previous ESB and the choice.

Shortly thereafter, the extinction experiment with the removable lever was repeated and it was found that a few free stimulations during the lever-out period would increase the number of extinction responses which appeared later after reinsertion (Pliskoff and Hawkins, 1963a); this was considered a further support of the drive-induction view. However, these authors also found evidence contradictory to any simple version of the drive-induction view. In one of their experimental groups, the lever was periodically removed and reinserted after a fixed period of time during the whole training period. After this kind of training, the animals did not show extinction as a function of time alone. In fact, this group showed fewer extinction responses if extinguished immediately after a bout of self-stimulation than if extinguished at the time of lever reinsertion.

Herberg (1963b) also found evidence against the oversimplified drive-induction view. He utilized sex-related and food-related self-stimulation points in two different groups. In each case, ESB yielded the appropriate consummatory response, and the self-stimulation rate was a direct function of the appropriate drive. With ESB in such points, Herberg argued, normal drive manipulations (such as deprivation or manipulation of hormones, should be sufficient to create drive, and the induction by ESB itself should be unnecessary. However, even in the cases where responding was a function of the appropriate drive, extinction was not. High drive levels could increase the rate of the self-stimulation response, but the did not add materially to the number of responses in extinction. Therefore, argued Herberg, it did not seem reasonable to suppose that the rapidity of extinction was due entirely to a deficit in the appropriate drive. He also showed that there was more responding in extinction if a fixed ratio schedule, rather than a continuous reinforcement schedule, was used, and that a rat habituated to 3-min bouts of self-stimulation yielded a very large extinction output if the experimental period was suddenly shortened to 15 seconds. The work of Pliskoff, Hawkins and Herberg might be summarized by arguing that any manipulation which served to foster an expectancy of reward during the extinction period improved extinction output, and, therefore, that expectancy of reward was as important as ESB-induced drive in determining extinction rates.

The converse of the latter argument is that the rapid drop-off in rates during extinction might derive from a rapid drop in "expectancy" rather than a sudden drop in "drive." Herberg said that overlearning resulted from (1) the short response-reinforcement interval, (2) the large number reinforcements usually applied, and (3) the repeated "bouts" of acquisition (i.e., periodic reconditioning), and this could account for the rapid drop-offs. Herberg also pointed out that "air licking" experiments in which a thirsty animal is apparently reinforced by licking a jet stream of cold air (Hendry and Rasche, 1961) provide the only instance of comparable activity "subject to as prompt and frequent reinforcement" as self-stimulation. Air-licking also shows rapid extinction.

In a recent exchange of letters, Deutsch (1963b) appeared to disclaim the simplified version of the drive-induction hypothesis, and Pliskoff and Hawkins (1963b) suggested an alternative explanation of rapid extinction; "It is entirely possible that behavior maintained by brain stimulation is unmotivated and that such behavior indicates the effects of a pure reinforcer." If this were the case, they argued, the behavior would be entirely under stimulus control, and the aftereffects of the preceding brain stimulus would make up an important part of the SD for the discriminated operant. The rapid extinction would then be explained by the well known fact that the effects of

a stimulus fall rapidly over time.

Differential Reinforcement of Low Rates

With electrodes in the very powefully reinforcing medial forebrain bundle region, Brady and Conrad (Brady, 1958b; 1960; Brady and Conrad, 1960a; 1960b) observed a disrupting effect on the timing behavior involved in a drl schedule. In one case, they arranged the program so that only the first response after a 20-second pause would be reinforced. A monkey working for sugar pellets eventually spaced responses so that the required 20 seconds often elapsed between them and thus it obtained a reward frequently. Working on alternate days for ESB reward, the same monkey seemed unable to pause. Its responses were inefficiently timed; about 100 responses were required for each reinforcement, and a wasted burst of responses, lasting for about 10 minutes, occurred after each reward.

Secondary Reinforcement

One experiment which involved "secondary reinforcement" was reported by Stein (1958). A food or sex reward not only motivates behavior but also imparts motivating power to neutral stimuli with which it becomes associated. The dog comes to a whistle because this "secondary reinforcement" has been associated with some primary reward. Stein found that, in similar fashion, a neutral tone associated with an ESB reward stimulus acquired reinforcing value for the rat; he speculated on the possibility that the pairings of tone and stimulus in some way empowered the tone to elicit activity in the neural tissues near the electrode tip.

Comparison Techniques

The obstruction box experiment is normally used to compare the intensity of different positive reinforcers by matching them against a measurable negative reinforcement. The animal is required to cross a grid which yields a quantifiable foot shock in order to get positive reinforcement. In a box where rats unfed for 24 hours would take a 60- to 180-μa foot shock for food reward, an undeprived implanted animal took 60-μa of foot shock for a stimulus of twice the threshold value in the medial forebrain bundle, and a 425-μa foot shock for a stimulus of ten times the threshold in the same system (Olds, 1958e; Olds and Sinclair, 1957).

The obstruction box also provided one method for comparing the different intensities of reinforcement produced by stimulation at different places. It was thought that even though a rat responded more slowly for olfactory-cortical stimulation than for MFB stimulation, the former might be more reinforcing; e.g., it might have a long enduring effect which would slow the animal down. In one experiment, a group of animals with olfactory-cortical electrodes was compared with a group with electrodes in the medial forebrain bundle. The same brain stimulus intensity was used in both cases. Within each group, intensity of reinforcement, as measured by grid crossing, was directly related to intensity, as measured by response rate. The MFB stimuli which showed greater intensity by producing higher response rate also showed greater intensity by causing rats to traverse the greater shock obstruction. However,

the most intense olfactory-cortical reward placement produced lower response rates but better grid crossing than the least intense MFB placements. Thus it was evident that response rates, while useful, were not perfect for measuring reinforcement (Olds, 1958d; Olds and Sinclair, 1957).

A similar point was made in a series of preference experiments (Brady, 1961; Hodos and Valenstein, 1962; Stein and Seifter, 1961b). In the first of these, advantage was taken of the fact that a monkey may balk or slow down if a lesser reward is offered after a more intense one (Tinklepaugh, 1928). Testing the same animal, with the rewarding brain stimulus delivered first to one area then to another, Brady (1961) varied the order of the points tested from day to day. He found that the animal would not work for olfactory-cortical stimulation after MFB stimulation, anterior medial forebrain bundle after posterior MFB stimulation, and so forth. With this technique, Brady worked out a hierarchy of structures according to the positive or negative reinforcing value of stimulation. This hierarchy, worked out by comparison techniques on monkey, is remarkably similar to those worked out by operant techniques on cat (Wilkinson, 1963) and rat (Olds and Olds, 1963).

In a more recent study, Hodos and Valenstein (1962) criticized response rates as a measure of the reinforcing value of stimulation in different brain areas. They showed that in a choice test, if a mild brain stimulus in a preferred area was compared with a strong brain stimulus in a nonpreferred area, the stimulus producing the highest rate was not always the preferred stimulus. However, when the same current was used in all tests, the areas yielding the greatest reinforcement by rate and preference tests were the same. The most interesting outcome of this preference study had to do with high-intensity stimulation: Even when rates declined at higher intensities, the higher intensities were usually preferred. The fact that response rate sometimes declined as the intensity of stimulation increased was borne out by other studies (Olds et al., 1960; Porter et al., 1958).

Valenstein and Beer (1962) showed by other techniques that when current was so intense that increments in stimulus level no longer produced increments in self-stimulation rate, there was still evidence of greater incentive value in the higher stimulus levels. The demonstration was made by showing that animals would risk more foot shock or go thirsty longer for the more intense ESB incentive. This happened even in cases where current levels were so high that they actually produced decrements in self-stimulation rate.

Applying a choice technique, Stein (1961b) permitted concurrent stimulation. Animals with two pedals could work them alternately or in any order they michg choose to stimulate two different brain points. Stein showed that rats maintaining high rates on each electrode separately could be made to work twice as hard to stimulate the two concurrently. For example, when presented with lever A alone to stimulate electrode A, one rat regularly maintained a 1500-rph rate. When offered at the same time lever B to stimulate electrode B, the rat maintained the 1500 rph on A, and, by racing back and forth, maintained a similar rate on lever B concurrently. Behavior at one pedal was often largely independent of behavior at the other, although interesting interactions were shown in certain cases. Posterior points in the MFB usually required less current for the same rate than that required by anterior ones.

In a study comparing different dependent varialbes, Deutsch and Stifler (cited in Deutsch and Howarth, 1963) reported that by special adjustment of

voltages, stimuli of different frequencies could be matched so that they appeared equally rewarding so far as preference test in a T-maze was concerned. When these stimuli were then used separately to reinforce running behavior, they no longer appeared equally rewarding. The frequencies were 60 cps, which is within the range normally used for brain stimulation, and 2000 cps, which is outside the range ordinarily used, and so high as to be considered relatively ineffective by most authors (cf. Ward, 1959b). The voltage of the higher frequency stimulus could be adjusted so that it was even preferred in a choice experiment; but it still caused running speeds much slower than those caused by the "nonpreferred" stimulus of 60 cps. Complicating the problem of interpretation was the fact that the voltage of the 2000 cps stimulus could be increased still further until it caused running of equal rapidity to that of the low-frequency stimulus. The authors concluded that the high-frequency stimulus accentuated reward aspects (preference) and the low-frequency stimulus accentuated drive aspects (speed) of two interdigitated systems. Because very intense stimuli are often preferred even though they seem highly ambivalent or conflicted and therefore cause slower behavior (Hodos and Valenstein, 1962), and because, even in cases where very intense stimuli cause behavior to slow down, further increments may cause behavior to accelerate again (Olds et al., 1960), it does not appear that the difference in frequency is needed to explain the phenomena reported. A mild but purely rewarding stimulus might be matched in preference tests with an intense but conflicted stimulus originating from the same electrodes, but the latter might cause slower approach behavior. Further increments in intensity might then tip the balance toward positive reinforcement and, again, speed behavior. Even if the latter explanation were in some degree correct, it does not seem impossible that selective penetration of particular brain systems by "resonant" stimulus configurations might participate in the generation of the observed effects, as the authors suggest. From the data, however, one might assume with equal justification either that the low frequency stimulus selectively engaged a "drive" (running speed) system, or that the high-frequency stimulus selectively affected a "drive" (aversive-and-slowing) system.

Satiation Tests

Another kind of test had to do with satiation or endurance. Behavior motivated by brain stimulation has sometimes been sustained for periods of more than 24 hours at a time. In long-run self-stimulation tests, it has been shown that animals with hypothalamic electrodes tended to respond to the point of physical exhaustion (Olds, 1958c) Animals with olfactory-cortical electrodes, on the other hand, tended to become satiated long before they reached the point of physical exhaustion. There was no satiation in either case if the animals were not allowed to exceed one hour of self-stimulation daily.

Qualitative Observation

Elicited effects observed by several investigators were thought to indicate positive reinforcement. MacLean (1957) reported that in olfactory-cortical areas of the cat, stimulation induced by depositing crystalline carbacol induced seizures which subsided after an hour or so. During subsidience, "enhanced pleasure and grooming reactions" were observed, and the cat was "unusually receptive to genital stimulation." Kopa, Szabo, and Grastyan (in

press) reported "a general relaxing effect" from stimulation in the centrum medianum of the thalamus, and occasional activation of alimentary reflexes as well.

Studies with humans have made reference to the patient's report of experience but these have been wague and ambiguous reports. Possibly this can be ascribed to the novelty of the experience. Sem-Jacobsen and Torkildson (1960) reported "feeling of ease and relaxation, feeling of joy with smiling, and great satisfaction." They spoke of " desire for repeated stimulation," and experience "ranging from curiosity and funny tickling to relaxation and pleasure." They allowed patients to stimulate themselves by pressing a button and found that "in some regions they like to keep the stimulus on for a prolonged period, only interrupted by short breaks. In other areas, the patients seem to get pleasure by frequently starting and stopping the stimulus."

"The most rapid rate of pressing and releasing the button," the authors reported,"was obtained when the patient's level of consciousness was altered in connection with self-stimulation. Frequently, as long as they were unresponsive and after discharges appeared in the record, they would press and release the button with a high repetition rate. Afterwards, they were unable to explain the behavior. We have never obtained any results similar to the rapid rate of 10 per second or more into which animals stimulate themselves." (It should be noted that animals rarely exceeded two or three responses per second, and that typical rates with olfactory-cortical electrodes were of the order of one response every several seconds.) Finally the authors indicated that "from strong pleasure areas we have found that the patients stimulate themselves into a convulsion. In the post-ictal (post convulsive) stage these patients were lying relaxed, smiling happily, contrary to the restless fighting frequently observed in patients after electronic treatment."

Neuro-Psychological Interactions

Arousal

The possible relation of the arousal system of Magoun (1950) to psychological mechanisms of drive has been, from the beginning, a matter of considerable conjecture. The postulation of a general emotional variable whose rise, fall, or steady states control reinforcement mechanisms is a common property of otherwise divergent psychological theories. Hull (1943) proposed that a high emotional state constitutes negative reinforcement, and that its abrupt decline constitutes positive reinforcement. Hebb (1955) suggested instead that a state of mild emotion fosters organized behavior and that the absence of emotion or extreme emotion is detrimental to this state of organization. The latter notion was extrapolated to the view that mild emotion constitutes positive reinforcement, and that strong emotion constitutes negative reinforcement (Sharpless, 1958). Magoun's reticular activating system (RAS) seemed to provide a physiological substrate for a general emotional mechanism and thereby added credence to theories of this type (cf. Lindsley, 1951). Schlosberg (1954), on the other hand, objected that the dimension running from sleep through alert attention to extreme tension which appears to be under reticular

control is but one dimension of emotional experience. As another dimension he mentioned pleasure-pain, which might be under control of different physiological mechanisms.

It is easy to see how this argument led to a study of physiological and anatomical relations as soon as brain points yielding positive and negative reinforcement were uncovered. The Hullion theory suggested that an arousal system might inhibit it. The Hebbian theory suggested that low level stimulation of an arousal system might cause positive reinforcement and high level stimulation negative reinforcement. Experiments (Glickman, 1960; Olds and Peretz, 1960) did not support either of these views but suggested instead that three different systems might exist in the midbrain: (1) a system where stimulation caused negative reinforcement and cortical arousal at all suprathreshold electric current levels; (2) a system producing positive reinforcement at all current levels, but requiring intense stimulation to produce cortical arousal; and (3) possibly a small area which yielded neutral arousal with no positive or negative motivational effects. Confusing the issue, however, was the fact that near to the neutral points there were also points which yielded positive and negative reinforcement simultaneously: if these were perfectly balanced at some points, one might get the appearance of neutral arousal.

Two possibilites therefore remained. The most likely was that three different physiological substrates exist: One where stimulation evokes positive reinforcement, one where it evokes negative reinforcement, and a third where it evokes physiological arousal. The alternative still existed, however, that no area yielding neutral arousal exists -- that all emotion-provoking brain-stimuli and all physiological substrates were intrinsically either positive or negative in emotional tone.

Arrest

Hunter and Jasper (1949) studied petit mal - i.e. the cessation of behavior and momentary loss of consciousness which appears in mild epilepsy. They found that stimulating certain brain points caused similar episodes of "arrest" in animals. These reactions have for various reasons seemed possibly related to the reinforcing mechanisms. First, in maze experiments (Olds, 1956b) where positive reinforcement was produced by application of stimulation to some olfactory-cortical structures, it was observed that application of the reinforcing stimulus in mid-maze caused an abrupt pause. The animal stopped in midbehavior for a variable interval, depending on the site of stimulation. It was first thought that some correlation of arrest and reinforcement might exist, but upon analysis it was found that the anatomical points of longest arrest were also points of least reinforcement. Later it was found that stimulation in the posterior focus caused no arrest at all.

Porter et al. (1959) also noticed the arrest phenomenon in conjunction with self-stimulation in an olfactory area of the thalamus which yielded mild positive reinforcement. In this case, after discharges in olfactory-cortical areas accompanied self-stimulation and these were always accompanied by the petit mal-like arrest reaction.

Many commentators have referred to the autogenic seizures; these are petit mal states which certain epileptic patients bring on themselves, seemingly on purpose (Bickford, 1953) It has been suggested that this association of

petit mal-like states with self-stimulation is an intrinsic rather than an accidental correlation (Morrell, 1961; Nielson et al., 1958; Porter et al., 1959). Sometimes it is suggested that the petit mal state is relaxing or pleasant (Morrell, 1961), or that it provokes automatic response repetition somehow related to a retrograde amnesia (Nielson et al., 1958).

Considering the large amount of self-stimulation that occurs without arrest or seizures and the multiplicity of phenomena that appear under the self-stimulation label (cf. p.12, Dependent Variables), it appears wise to take a very broad view. Self-stimulation can occur with or without seizures; and seizures may be positive or negative in emotional aura, depending probably on anatomical locus of the focal lesion. Occasionally, self-stimulation may be directed toward a "forgetting of pains" intrinsic to spreading seizures generally, but this is certainly not usual.

Perception

Perhaps the best answer to the seizure question is the demonstration by Beer and Valenstein (1960) that the animal can be alert and attentive during self-stimulation. These investigators established hypothalamic self-stimulation behavior in hungry animals which had previously been trained to discriminate between two tones, one of which signaled the availability of food. The tones were then presented for discrimination during the actual brain stimulation interval of the self-stimulation test. The tones started after the onset and terminated before the end of the reinforcing stimulus train. Even under these conditions, animals discriminated the tones well and stopped to eat when the food-related tone appeared.

Learning

While perception occurred during hypothalamic self-stimulation, it was not at all clear whether some confusion of learning or associative mechanisms did not occur, at least with the self-stimulation electrode in certain areas. Maze experiments first indicated that while rats moved faster for a ventral telencephalic reward, they still learned more slowly than if the reward were food. Some confusion from the brain stimulus was suspected (Olds, 1956b).

Stein and Hearst (1958) demonstrated quite clearly that the rewarding brain stimulus in some olfactory-cortical, olfactory-midbrain boundary areas had a severely retarding effect on acquisition of a discrimination habit if presented during instead of after completion of learning. In this experiment, a hungry animal got food by pressing one of two levers. Auditory stimulus A signaled availability of food at the left lever; auditory stimulus B signaled food at the right lever. For different rats, rewarding brain stimulation accompanied the onset of one of the two stimuli (A for one rat, B for another). In each case, the animal learned far more slowly to respond to the stimulus which was accompanied by the rewarding ESB. About 75 trials sufficed for perfect responding when the ESB was withheld. After 250 trials, responding was still far from perfect when the ESB accompanied the auditory stimulus.

In another study (Olds and Olds, 1961), a wide sampling of brain points was tested for disrupting effects of ESB on a discrimination reversal prob-

lem. In this case, after extensive pretraining, the animal would learn and relearn approximately the same problem day after day in practically the same number of trials. Food reward was given on a contingent basis after the correct response. Brain stimulation was given on an uncontingent basis in $\frac{1}{2}$-second trains every 3 seconds all during the test procedure. Stimulation in hypothalamus and rhinencephalic structures caused disruption. Stimulation in neocortex, primary sensory systems and many tegmental areas did not. This led to a supposition that disruption was correlated with rewarding effects of electric stimulation. The supposition was confirmed by implanting rats with electrode pairs in the lateral hypothalamic self-stimulation areas and in the dorsomedial tegmental escape areas. After pretests to confirm elicitation of strong emotional responses, each animal was tested for learning; first, during stimulation of one elctrode pair, then for learning during stimulation of the other. In all cases, animals learned quickly under the negative reinforcing stimulation; learning was totally disrupted by stimulation at the rewarding point.

It has been suggested that these findings have more to do with the reinforcing properties of the stimulus than with any direct relation of the brain points to associative mechanisms. In a standard reinforcement experiment, reward was applied on a contingent basis. If the animal makes the correct response, the reward occurres; otherwise, it does not. In such a case, the reward fostered correct performance. Reward applied on an uncontingent basis during problem solving had a less certain status. Several experiments (Bush, and Mosteller, 1955) have shown that a distribution of reinforcements on the basis of some ration between the wrong and the right response eventually caused a similar distribution of responses. It has been suggested (H.F. Harlow, personal communication) that this might be spoken of as partial reinforcement of the wrong response, and that this principle applies to the cases where learning seems to be inhibited by a rewarding stimulus. The animals received the positive reinforcement of brain stimulation for both right and wrong responses with the additional reward of food for the right response. This partial reward of the wrong response perhaps did account for the animal's failure to eliminate the error from their repertory.

The possible objections to this simple explanation also need to be voiced. First, such an explanation certainly could not be applied to recent reports of impairment of discrimination learning by lesions in some of the same self-stimulation areas (Thompson, 1960). Second, it is interesting, if partial reward of wrong responses caused impairment, that partial punishment of right responses by dorsomedial tegmental stimulation caused no similar impairment. Third, this explanation does not account for the faster running but slower learning of the early maze experiments (Olds, 1956b), nor for the confusion caused in the Stein and Hearst (1958) experiment where the wrong response was not reinforced at all. These arguments tempt one to suppose that some real confusion of associational processes occurred as a result of excessive stimulation in reinforcing areas.

It is perhaps possible to bring the two lines of explanation together by arguing first that uncontingent or excessive escitation of positive emotional mechanisms of the brain had a far more disorganizing effect on choice behavior than similar excitation of negative emotional mechanisms. On the other hand, the same positive stimulus applied on a normal and contingent basis caused maze learning, as indicated earlier; thus it can cause organization of associative processes. From these two points it is perhaps not too great a leap

of thought to suppose that the positive-reinforcing mechanisms have far more control over the associative processes that guide behavior at a choice point than the negative ones.

Social Interaction

Delgado (1963) introduced brain stimulation into a monkey colony. Of particular interest was a taming and possibly reinforcing stimulation of the dominant male. The stimulation produced a diminution or cessation of eating, drinking and aggressive responses but no similar diminution of "nestling" with a partner. It also tamed the animal making him easier for the experimenter to handle. In a "heterostimulation" test it appeared that one of the three other monkeys in the colony learned to press a lever to tame the dominant male. Response rates for the animal that learned increased from 12 to 24 per day on days 2,3 and 4 of "acquisition" when each response caused a 5-second radio-stimulation of the dominant male. But on six "extinction" days when the same response did not cause any stimulation the rate fell to 9 on the first day and to 8 or lower on the remaining days.

The Electric Stimulus

While the technical problems of electric stimulation are interesting, it is now clear from the work of Ward (1959b) Keesey (1962), and Miller and his colleagues (Miller et al., 1961) that for self-stimulation experiments details of pulse shape and frequency, once deemed important (Lilly et al., 1955), are relatively unimportant.

Direct current stimulation causes injury to tissues. It is most injurious if given continuously for several seconds, in which case it makes a major electrolytic lesion after one application. Even if given in one millisecond pulses separated by 10 to 15 milliseconds, it produces cumulative injury. If, however, ordinary alternating current, or any special positive and then negative pulse series, is used, cumulative injury does not occur within the range of parameters employed in the experiments reported here (Miller et al., 1961). When such a series of pulses is used, each stimulation is composed of a train of pulses. Each pulse in the series has an intensity and a duration; besides this, the whole train has a longer duration and a repetition rate of pulses which we speak of as a frequency. As far as the individual pulses are concerned, it appears that within the range normally used the peak intensity, which is best measured in milli- or microamperes, is more important than the duration of these pulses in determining the extent of the effect in the brain (Ward, 1959b). On the other hand, the duration of the train of pulses is quite important, even though the duration of each pulse in the train is relatively unimportant; apparently longer trains provide more stimulation than short ones because they provide more pulses (Ward, 1959b). When spoken of as frequency, the pulse repetition rate conjures notions of resonance in most brain-and-behavior investigators; however, evidence of particular optimal frequencies has not been found. Pulse repetition rate is important in the sense that a faster rate yields more pulses for the same train duration. It is also clear that there are repetition rates so fast as to be relatively ineffective, probably because of the time involved in the neuron recovery cycle. Frequen-

cies up to 5000 pulses per sec (pps) have been shown to be effective (Brown and Cohen, 1959); at the other extreme is the unusual case of single pulse rewards of several milliseconds duration, which have also been found to be effective (Olds and Tullsen, unpublished). However, there is a sharp drop in efficacy at the upper end of the spectrum between 300 and 1000 pps, and at the lower end somewhere below 10 pps. Thus, single pulses and frequencies of 2000 pps are relatively ineffective. Ward (1959b) found that there was a wide range of optimal frequencies in the 40-200 pps range when sine wave stimulation was used.

Interesting findings have emerged from studies concerned with the "amount of stimulation," which is mainly the intensity of the stimulus measured in microamperes or the duration of the train measured in seconds or fractions thereof. Increments in the stimulus caused by adding to the electric current might be expected to have different effects from increments caused by adding to the duration of the trains, as one would expand the stimulus field in the brain and the other would increase the duration of excitation in the same field.

Studies involving changes in electric current levels have regularly shown clear-cut thresholds and a variety of functional relations as current was increased beyond threshold levels (Olds et al., 1960; Reynolds, 1958; Sidman et al., 1955). With electrodes in some MFB locations, response rate was augmented by each increase in electric current, up to the point of maximum possible rate, and then no decline was observed even when increases were made up to 16-times threshold (Olds et al., 1960). With other electrodes in some olfactory-cortical pathways, responding never rose above the low levels which appeared at threshold; the same rates appeared at threshold and at 16-times threshold. With electrodes in hypothalamic nuclei (between the olfacto-midbrain pathways), response rates were augmented by stimulus increases up to some current level; further increases caused response rates to decline more or less steadily (Reynolds, 1958). In other cases (see Fig. 3), the decline was not steady; response rate showed a series of rises and falls as current was increased (Olds et al., 1960). In both cases, the optimal current level was relatively stable for a given electrode placement, and the response rate for any given current level was stable. In preference and other comparison studies (Hodos and Valenstein, 1962; Valenstein and Beer, 1962), it was demonstrated that animals often preferred the higher intensities even when they responded equally or more slowly for them. One experiment with self-regulatory current levels, however, showed that animals with posterior hypothalamic electrodes often preferred less than maximal current levels, whereas animals with olfactory-cortical electrodes often preferred the maximal current levels, levels which regularly produced seizures (Stein and Ray, 1959). Even with the posterior hypothalamic electrodes, where preference was for less than maximal stimulus intensities, the current levels preferred were very high, much higher than an experimenter would normally use.

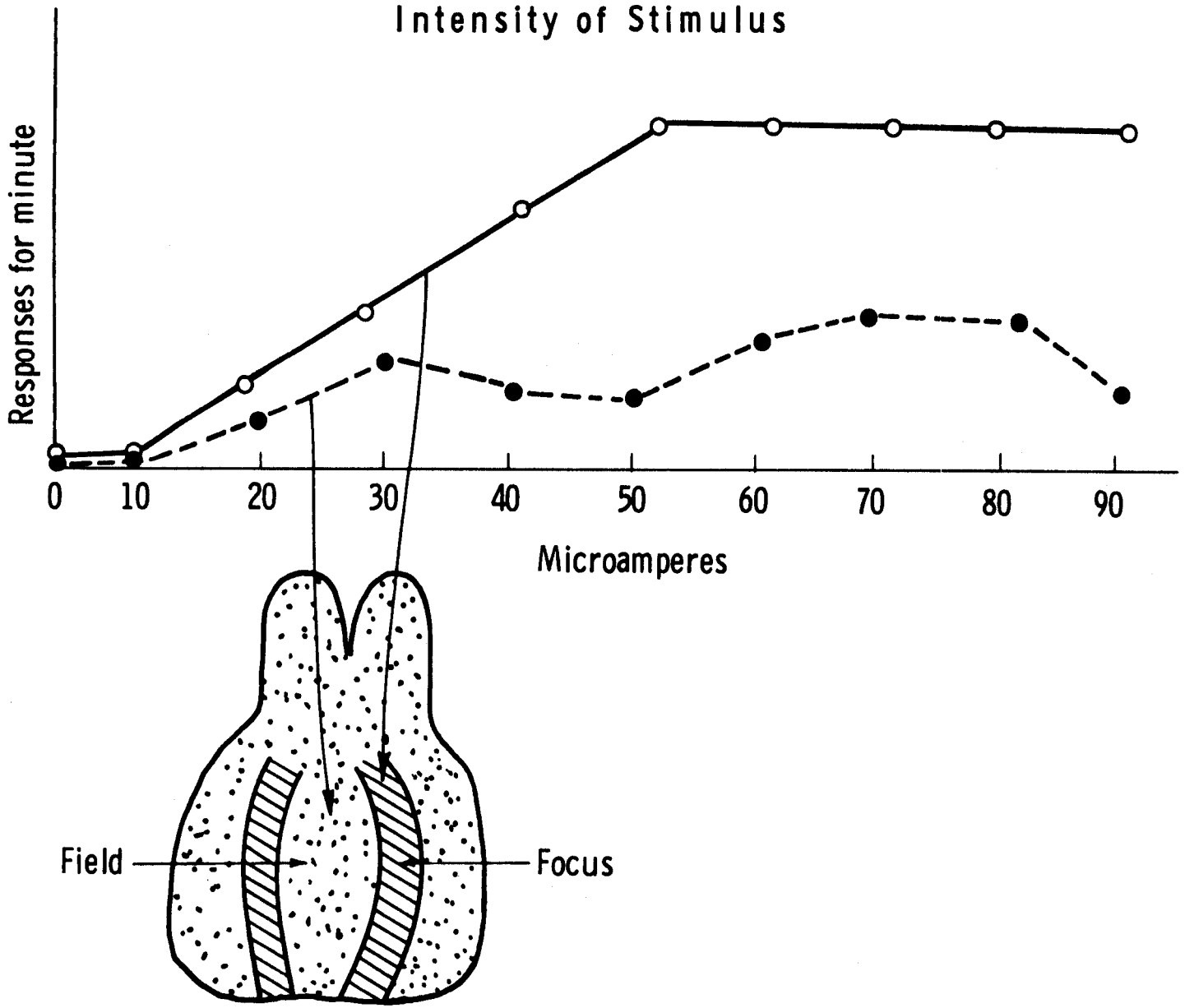

Intensity of Stimulus
Responses for minute
0
10
20
30
40
50
60
70
80
90
Microamperes
Field
Focus

Fig. 3

Figure 3. Electric current functions in self-stimulation. With electrodes in the focal area (solid line) increments in current often produced regular increments in self-stimulation rate up to a maximum possible response level. Further increases in current did not cause any further changes in rate. With probes in other areas (e.g. between the two focal areas) some increments in the stimulus caused increments in rate, further rises in the stimulus level often caused rate to decline. But with the current set at still higher levels the rates often rose again.

The work of Nielson et al., (1962) indicated that an ESB delivered to any tested brain area provided a distinctive cue to the animal, regardless of its other effects. Campbell (1963) showed that with electrodes in reward substrates, thresholds for this cue function were regularly lower than thresholds for self-stimulation. Thus, animals showed by discriminative behavior that they could detect current levels which were too low to maintain stable self-stimulation behavior. Morgenson and Morrison (1962) found that the cue function was also demonstrable at levels above the self-stimulation threshold; they did this by showing that a rewarding ESB could be used as the conditional stimulus for an avoidance response.

The problem of determining thresholds of self-stimulation has been discussed by Valenstein (in press, 1964). Three methods have been used; each had drawbacks. One was successive presentation of current levels in a rising series (Olds et al., 1960; Olds and Olds, 1963); in this case, as Valenstein pointed out, the animal might respond anticipatorily to the cue properties of the ESB before the reward threshold was actually crossed. In another case, there was random presentation of different current levels (Valenstein, in press, 1964); here the effect of Crespi (1942) created a problem, i.e., animals responded more poorly to a low but suprathreshold ESB if it followed a higher and more preferred ESB. In an experiment with self-regulation, animals were trained to indicate a "threshold" level by their own responses (Stein and Ray, 1960). The electric stimulus was started at a predetermined "maximum" level; each response caused a brief ESB and also caused the stimulus to be reduced by one step. By slight additiona effort, the animal could, at any point, press a reset lever which started the cycle again with current at the prefixed maximum. The stimulus value at the time of reset was taken as "threshold." This value was quite stable over time for a given electrode placement, and was a dependable function of pharmacological variables. However, even though stable values were achieved by this method, it is not at all clear that these were threshold values. The animal preferring high intensity stimulation might easily have reset long before ESB was reduced to the threshold level.

Thresholds have been used mainly as an alternative to response rates in assessing the reinforcing power of ESB in different brain areas and under different drug and drive states. For these purposes, both the orderly presentation of incremental series and the self-adjustment technique have provided relatively satisfactory tools because in a given experiment the same method was used in all cases.

The problem of train duration and the frequent repetition of trains has received preliminary study (Olds, 1960b; Roberts, 1958b; Stein, 1962a; Valenstein and Meyers, 1964). Stein (1962a) showed that with posterior electrodes in or near the olfactory-midbrain pathway, animals usually selected very brief trains of considerably less than 1 second. When electrodes were placed in olfactory-cortical pathways, trains of 1 to 9 seconds were selected. With electrodes in cingulate cortex, trains of indefinite duration were selected (unpublished observation). Roberts (1958b) showed that very long ESB's (3 minutes) were sometimes aversive with electrodes in the posterior part of the olfactory-midbrain pathway while short (0.5 second) trains produced positive reinforcement. With other electrodes in approximately the same region, even 3-minute trains produced positive reinforcement. In a similar study, Valenstein and Meyers (1964) showed that animals with olfactory-cortical electrodes took more stimulation when intervals of 1.5 seconds or more intervened between trains. Animals with electrodes in olfactory-midbrain pathways sometimes took continuous stimulation. Two other studies have suggested that two frequent repetition of pulses in olfactory-cortical areas might have negative effects. Asdourian (1962) performed an experiment in which a glucose solution was administered via a drinking tube. When each contact with the drinking tube was also reinforced by "positive" stimulation in olfactory-cortical pathways, the amount of glucose consumed was reduced. Valenstein (in press, 1964) similarly reported that when a rat responding rapidly on a ratio schedule for food reward was given one olfactory-cortical ESB after each response, the response rate was slowed. He also showed that a rat responding regularly for the ESB was slowed when some responses were also reinforced with food; he thought this might be due to the time spent eating. In another experiment, a variety of brain points were tested, first, for self-stimulation, and second, for responding to terminate a series of $\frac{1}{2}$-second trains repeated at one per second. Because many ESB's which produced self-stimulation also produced responding to terminate the series, it seemed that either the ESB produced a very confused and mixed reaction, or that infrequent trains were positive but too frequent trains were aversive. It also appears, however, that positive reinforcement sometimes became attenuated if trains were too widely spaced: animals in a runway moved faster for brain stimulus if the trials were spaced 20 seconds apart than if 15 minutes intervened (Seward et al., 1960).

Poschel (1963) has recently answered one question that enjoyed a temporary vogue, namely, whether the onset or termination of the ESB provided the positive reinforcement. He provided ESB with sudden onset and gradual termination, and vice versa. Because the current with sudden onset produced stronger positive reinforcement behavior than current with sudden termination, he concluded that the positive reinforcement commenced with the onset of the ESB.

Punishment and Reward

The characteristic behaviors associated with the primitive property of irritability inherent in living matter are negative-avoiding reactions. These aversive reactions are far simpler to explain on a cause-and-effect basis than are appetitive or homing reactions. Possibly because of this, a tendency to parsimony has led to many attempts to show or suggest that the seeming appetitive reactions are nothing but aversive reactions in disguise (Miller, 1957a; 1958; 1961a)

Direct experience, on the other hand, at first makes it appear that reward and punishment are quite different mechanisms for controlling behavior. Yet, even in experience, these mechanisms rarely appear in conflict; pleasure and pain are rarely reported simultaneously, and the same behavior often seems aimed at the avoidance of punishment and the pursuit of reward. If the mechanisms are dual, some method of interaction or reciprocal correlation seems to be worked out within the organism to prevent conflicts.

Experiments in which aversive reactions were produced by electric stimulation of the brain have yielded quite definite information about anatomical structures peculiarly related to mechanisms of negative reinforcement. These have recently been combined with studies of positive reinforcement to further the analysys of relations between mechanisms of punishment and those of reward

Many studies which show elicitation of appetitive and aversive reactions from stimulation of the same point have been taken as evidence for a single- rather than dual-motive mechanism; studies which show differentiation of appetitive from aversive points have been taken as evidence for a dual-motive mechanism. Studies of interactions have suggested possible mechanisms of reciprocal correlation.

Escape Reactions

In early reports, stimulation of a wide area surrounding the posterior part of the olfactory-midbrain pathways in cat was reported by Hess (1954a; 1954b) to elicit a pattern of attack-defense. Recent work on cat and monkey (Delgado, 1955; Delgado et al., 1954; Delgado et al., 1956; Roberts, 1958a; 1958b; 1962) indicate painlike responses and avoidance responses from a variety of midbrain areas. Similar responses have also been reported from related structures in the thalamus. A fearlike response characterized by avoidance behavior has been reported from stimulation in a different thalamic nucleus (Roberts, 1962). Similar responses have also resulted from electric stimulation applied to some parts of the hypothalamus. Rage has been produced with electrodes in other parts of the hypothalamus (Masserman, 1941; 1942; Roberts, 1958b) Many parts of the olfactory cortical system have also been implicated in negative reinforcing effects of ESB (Delgado, 1955; Delgado et al., 1954; 1956) In a recent study of rat (Olds and Olds,1963), ESB effects were categorized as purely positive, purely negative, and mixed positive-negative. The area where stimulation caused purely negative reinforcement was found to follow two courses from midbrain into forebrain. One was spoken of as a periventricular system because it followed the boundaries of the cerebral ventricles, which occupy a midposition throughout much of the

brain. The other was clearly interdigitated with somesthetic, visual, and auditory sensory systems.

Ambivalent Responses

Roberts first reported rewarding and punishing effects of stimulation of the same electrode at the same intensity. He came upon the effect while investigating a boundary area of the posterior olfactory-midbrain pathways. He found that electric stimulation caused escape behavior after the onset, but that the animal would not heed a warning signal and avoid prior to brain stimulation (Roberts, 1958a) Roberts first guessed that for some reason the brain stimulus failed to become associated, by normal learning mechanisms, with the warning signal. Later, however, he tested the notion that the animal might be rewarded at first by the onset of the stimulation, and then punished by its continuation (Roberts, 1958b). Proceeding on this assumption, he found that animals would press a lever to turn the stimulation on, and would also respond to turn it off. Using a symmetrical Y maze with one alley for "on," one for "off," and one for leaving the stimulus "as is" whether on or off, he found that these animals would work to turn on and then to turn off the same stimulus. At low intensities, the turn-on response was dependable and the turn-off response nearly random. As the intensity increased, the turn-off response became dependable and the turn-on response became slower and more conflicted.

His conclusion, therefore, was that brief or low-intensity stimulation was positively reinforcing but with increased intensity or prolonged duration the positive reinforcement became less and a negative reinforcing component of the stimulus appeared.

In this, as in the other approach-escape experiments, identical or roughly similar stimulus intensitites were used in reward and punishment tests. Characteristically, however, the train duration has been fixed at some brief level during reward experiments, but has been continued until response occurred in escape experiments; thus the duration is usually in the escape or avoidance experiments.

In the same study (Roberts, 1958b) a special test was made to assess the duration factor. Animals were forced to take a 3-minute train of stimulation or none at all. Under this regimen, two animals showing milder reward in previous test chose none at all, while one animal which previously showed strong reward took the 3-minute stimulus. For two of the animals, therefore, extending the duration of the stimulus transformed it from positive to negative.

The one case rewarded by the longer train was taken seriously, however, for it supported an important argument; namely, that the onset of the hypothalamic stimulus was in itself a rewarding event. Some earlier arguments had suggested that animals apparently pressing for such stimulation were in fact rewarded by its cessation.

The work of Roberts was followed by that of Bower and Miller (1958), who reported that rats with electrodes in the anterior part of the olfactory-midbrain pathways would work both to approach and to escape from electric stimulation, but that rats with electrodes in a posterior part of this same

bundle showed pure approach behavior.

Brown and Cohen (1959) implanted electrodes in areas of the hypothalamus of cats which yielded classical "hypothalamic rage." They showed that cats would respond faster on successive trials to get a 0.3-second train of stimulation at these points, and would also escape from a similar but more enduring train of stimulation at the same point when the stimulus was continued up to the time of the escape response. These animals, unlike those of Roberts, did learn to heed a warning signal, and eventually, many of them responded early enough to avoid the enduring stimulation altogether. It has been argued that in this experiment the same stimulus was employed in the approach and avoidance experiments but a careful perusal of the data suggests that the average duration of the stimulus which provoked avoidance behavior was at least 6 times that of the approach stimulus. It might be argued that in the escape-avoidance experiment the animal might have had a briefer stimulus by leaping the barrier sooner but experience in our laboratory suggests that animals rarely develop the skill to cut off a stimulus in less than a second after its onset. The authors concluded that the stimulus had merely an activating effect without appetitive or aversive characteristics. But the data are possibly better interpreted by Roberts' assumption (Roberts, 1958b) of rewarding effects being associated with brief stimulation and aversive effects associated with more enduring stimulation at the same point.

Analyzing the midbrain of rats, Olds and Peretz (1960) found that stimulation in some "periventricular and sensory" points caused animals to escape from brain stimulation onto an aversive foot grid but caused no appetitive responses. Stimulation in some olfactory-midbrain pathway points caused strong appetitive behavior but no escape response, and stimulation in middle parts of the reticular activating system caused both the escape and the appetitive responses, depending on the nature of the test.

Utilizing a technique which permitted the same animal to press the same pedal (first, to turn on electricity in the hypothalamus, then to turn it off,and later to turn on electricity in the midbrain, then to turn it off), it was shown (Olds, 1960a) that some electrodes would yield reward but not punishments, while others yielded escape but not reward. Some electrodes, however, yielded both. In this case, the escape stimulus was nearly identical with the one used in the reward studies as both had the same train duration; however, in escape studies the trains were more frequent. The repetition of trains occurred at a rate of one per second unless stopped or postponed for 4 seconds by a pedal response (cf. Sidman, 1953; Travis and Olds, 1959). In reward tests, response rates of ambivalent rats were never above one response for every 2 seconds. Thus it appeared that having the stimulus applied too often was aversive in these cases.

Applying this dual-test technique to map the olfactory and related areas in rat (Olds and Olds, 1963; Wurtz and Olds, 1961), it was shown that electrodes on many of the boundaries of the positive reinforcement system yielded attenuated positive reinforcement but also yielded escape responses. However, the main region in which electrodes produced these ambivalent reactions was the group of nuclear masses which make up the medial hypothalamus; all of the medial hypothalamus, which lies between the olfactory-midbrain pathways, was involved. It was first thought that only boundaries between appetitive and aversive areas would yield the ambivalent reactions, but it was difficult to treat the whole medial area, which had long been considered the main body of

of the hypothalamus, as a boundary region of the medial forebrain bundle. In any event, because it was more than 2 millimeters across, and because ambivalent reactions occurred in the middle, it was no longer possible to contend that ambivalent reactions occurred only on the boundaries of the purely positive system. The ambivalent reactions also occurred with considerable frequency when electrodes were placed anteriorly in the medial forebrain bundle itself (Bower and Miller, 1958; Olds and Olds, 1963); in fact, purely positive cases were extremely rare with electrodes in the anterior hypothalamus or anywhere in the olfactory-cortical areas. This suggested that the positive system might be more diffuse and intermingled with other systems in anterior areas.

In all the ambivalent cases reported, it appeared that the stimulus became aversive if presented immoderately. This view is in harmony with work mentioned earlier showing that with electrodes in certain places a decline in positive reinforcement sometimes occurred at high electric stimulus levels (Hodos and Valenstein, 1962; Reynolds, 1958; Stein and Ray, 1959). We might conclude that with electrodes in certain places, a change from appetitive to aversive effects often occured on the basis of changes in the quantity of stimulation, i.e. either changes in duration of train, number of trains per unit time, or intensity of stimulus. There was a possibility that changes in duration were more important than changes in intensity.

Two papers suggesting change of reinforcement sign based on external factors have appeared. Nielson et al. (1958) indicated that using a neutral caudate stimulus as a warning signal of oncoming aversive shock converted the caudate shock to an aversive stimulus itself. Kopa, Szabo, and Grastyan (in press) reported that stimulation in diffuse thalamic areas caused increased fearlike behavior in an otherwise dangerous situation and increased relaxation in an otherwise safe situation.

In summary, for some cases the prime determinant of reinforcing effects was the locus of the stimulating electrode. Thus stimulation in some olfactory-cortical regions (Lilly, 1958a; Olds, 1960a) and in the medial forebrain bundle (Brodie et al., 1960b; Olds, 1960a) seemed irreversibly positive in reinforcing effects. Stimulation in a preiventricular system (Delgado, 1955; Delgado et al., 1956; Olds, 1960a; Olds and Peretz, 1960; Olds and Olds,1963; Roberts, 1962), or a primary sensory system (Delgado, 1955; Delgado et al., 1954; Lilly, 1958a; Roberts, 1958b) was irreversibly negative. For other points, particularly in medial hypothalamus, the amount of stimulation seemed the prime determinant of reinforcing effects with brief and low-intensity shock yielding positive reinforcement, and high-intensity or long-enduring shock becoming negative in reinforcement sign. Finally, some points in caudate and in diffuse systems of the thalamus seemed to take on a reinforcement sign either from associative learning or from other aspects of the situation.

Anatomical Relations of Punishment and Reward Systems

What can be concluded from the set of anatomical relations between points yielding positive reinforcement and points yielding negative reinforcement? At a very gross level, the most striking fact was the enormous differences between hypothalamus (the area of the olfactory-midbrain pathways) and thalamus (the area just above the hypothalamus, long known as the may relay station for cortex-bound messages of somesthetic, visual, and auditory systems). There

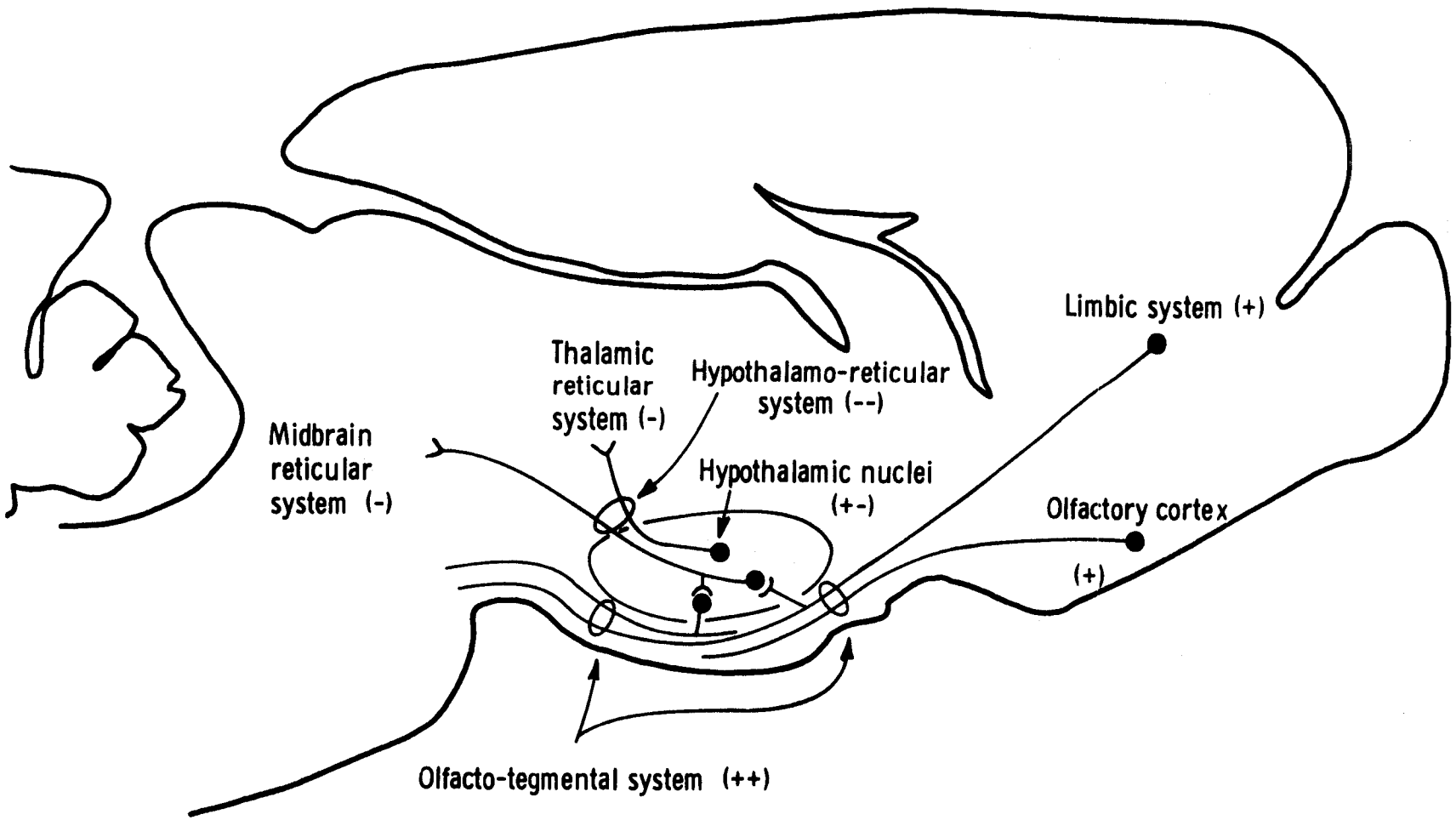

Limbic system (+)
Thalamic
reticular
system (-)
Hypothalamo-reticular
system (--)
Midbrain
reticular
system (-)
Hypothalamic nuclei
(+-)
Olfactory cortex
(+)
Olfacto-tegmental system (++)

Fig. 4

has been almost no evidence of unequivocal escape behavior produced by electrodes in the hypothalamus, and very little report of persistent self-stimulation with electrodes in the thalamus. Even though these statements are only approximately true, there is no doubt about the fundamental difference. At the very least, one is led to wonder about the evolutionary and functional significance of an arrangement which appeared to put negative reinforcement mechanisms mainly in thalamic systems and positive mechanisms mainly in hypothalamic ones.

At the level of detail, there are three surprising points: (1) the close "synaptic" relation of the "positive" and "negative" motive systems to one another; (2) the tendency to find "pure" effects in fiber bundles, and "ambivalent" effects in nuclei; and (3) similar thresholds and electric current functions for appetitive and escape behaviors in mid-hypothalamic locations (Olds and Olds, 1963).

It appeared quite possible that fiber bundles yielding positive reinforement regularly synapsed with those yielding negative reinforcement. Most definite were the findings (Olds and Olds, 1963) that the region of the medial forebrain bundle, which is the primary input to mid-line hypothalamic nuclei, yielded positive reinforcement; that the nuclei themselves yielded ambivalent effects; and that the periventricular system of fibers, which appear to be the main outflow of medial nuclei, yielded pure negative reinforcement (see Fig 4) Similar patterns appeared likely at other synapses, but these remain to be definitely validated. The hypothesis of inversion of sign, from input to output, of hypothalamic nuclei was strengthened by points (2) and (3) above. Ambivalent effects in such a case would be achieved from stimulation of the nuclei themselves because the stimulus would affect both afferents and efferents. And the field of afferents and efferents would be relatively homogenous, thereby accounting for the similarity of thresholds for the two effects.

Figure 4. This is a schematic picture of the connections (synapses) in the hypothalamus between medial forebrain bundle fibers and the neurones of the periventricular system (here called the hypothalamo-reticular system). Three groups of neurones appear: first are longer fibers from olfactory cortex (parts of which are here called the limbic system); they follow the medial forebrain bundle into hypothalamus and there synapse with fibers of the second system; the second system fibers originate in hypothalamus and travel upward toward emotional systems of thalamus and midbrain. A third group of fibers originates in hypothalamus and sends processes back into medial forebrain bundle; these fibers are shown here as being innervated by offshoots (collaterals) from the fibers produces pure (but mild) positive reinforcement; stimulation of the connection points (nuclei) in hypothalamus causes mixed

positive and negative reinforcement. Stimulation of the second group of fibers produces pure negative reinforcement. Finally, stimulation of the third group of fibers produces intense, pure positive reinforcement.

It has been proposed that a large number of direct synaptic relations between elements whose stimulation yields effects of opposite signs might indicate that one or several of the main projection pathways in this group of systems have an inhibitory rather than excitatory function.

From the anatomical data, one is led to think of a circuit (Papez, 1937) consisting of alternation P fibers (whose stimulation is positively reinforcing) and N fibers (whose stimulation is negatively reinforcing), all more or less spontaneously active and each exerting an inhibitory influence on the next neuron of the circuit. If such a system existed, it would function to mediate reciprocal inhibition of positive and negative reinforcing systems, and it would indicate the likelihood of a mechanism of action common to the two systems.

Interaction of Motive Systems

In one set of studies (Olds and Olds, 1962), animals were tested with positive self-reinforcement during continuous negative stimulation and with ESB escape behavior during continuous positive stimulation. The test for positive self-reinforcement was made by presenting a hypothalamic stimulus after each lever response during a 2-minute period while a constant train of stimulation was being applied to the negative reinforcing point in dorsomedial midbrain via a different electrode. The test for negative reinforcement was made by presenting repeated 1/2-second trains of midbrain stimulation at a rate of one per second and interrupting this sequence for 4 seconds after each lever response; this was done during a 2-minute period while a constant train of stimulation was being applied to the positive reinforcing point in olfactory-midbrain pathways via a different electrode.

The constant negative train, as might have been expected, impeded and sometimes completely inhibited the positively reinforced behavior. Hoebel and Teitelbaum (1962) reported a similar finding with stimulation in the ventromedial hypothalamic "satiety" center where stimulation also caused negative reinforcement (Olds, 1960a). Ventromedial hypothalamic stimulation inhibited self-stimulation via lateral hypothalamic electrodes; also, lesions at the ventromedial point caused an augmentation of the positively reinforced behavior (Hoebel and Teitelbaum, 1962).

Quite surprisingly, however, the constant positive train in olfactory-midbrain areas, far from impeding the midbrain escape behavior, regularly facilitated the negatively reinforced behavior (Olds and Olds, 1962). The asymmetry of the outcome appeared to indicate a one-way inhibition acting from the escape mechanism of the periventricular area on the reward system of the lateral hypothalamus. The finding also seemed to suggest that activity in the olfactory-midbrain "reward" point was synergistic with operant escape or avoidance behavior. In further experiments no similar synergistic

relation was observed when the uncontingent stimulation was applied in the olfactory cortical field of self-stimulation. Thus it appeared to indicate some special property of the self-stimulation focal region.

When midbrain escape behavior was tested with a constant train of stimulation in olfactory-cortical reward points, behavior was depressed instead of augmented (Routtenberg and Olds, 1963). Brady and Conrad (1960b) also reported that normal "fear" reactions failed to appear in either rat or monkey when the animal was working or brain shocks in some olfactory-cortical pathways. These animals, when working for food or water, stopped and cowered if a signal announced oncoming pain-shock. Working for olfactory-cortical brain shock, the same animals seemed to ignore the danger signal. The suggestion that such stimulation might cause relief of pain or fear was in good accord with reports of clinical investigators that stimulation in "septal" area (Heath and Mickle, 1960) or other anterior locations (Sem-Jacobsen and Torkildsen, 1960), in human beings caused relief and relaxation.

Effects of CNS Damage

Two studies utilizing surgical ablation and three using electrolytic lesions in relation to self-stimulation experiments have appeared. Also, extended studies of the effects of spreading cortical depression of the Bures (1961) type on hypothalamic approach behavior and tegmental escape have been made.

The studies of Ward (1959a, b, 1960, 1961) indicate that the olfactory-cortical areas are relatively unimportant to the basic phenomenon. He implanted electrodes in rewarding olfactory-midbrain areas and tested these (Ward, 1959a, 1960) after suction ablation of two different olfactory subcortical areas. Large lesions in both structures were often without influence on tegmental self-stimulation. Ward suggested that the various areas yielding self-stimulation subserved parallel rather than mutually prerequisite functions.

Data have now indicated that lesions in the posterior (midbrain) part of the olfactory-midbrain system attenuated or abolished self-stimulation via more anterior electrodes whether these were in the same system (Olds and Olds, in press, 1964) or in the olfactory-cortical system (Coons and Fonberg, 1963). Quite surprisingly, these "reward focus" lesions also caused attenuation or complete ablation of the escape behavior produced by stimulating the dorsal midbrain area, which is the area that receives fibers from the medial hypothalamus (e.g., from the "satiety center") Lesions in this dorsal midbrain area, on the other hand, sometimes augented self-stimulation when self-stimulation electrodes were placed in the posterior part of the olfactory-midbrain area (Olds and Olds, in press, 1964). Augmentation of lateral hypothalamic self-stimulation by lesions in the "satiety" center of the medial hypothalamus has already been mentioned (Hoebel and Teitelbaum, 1962). These data, together with those of Ward (1959b; 1960; 1961) showing that anterior lesions do not affect posterior self-stimulation, suggested that the positive reinforcement system had an anterior field in olfactory-cortical areas which might function by modulating a posterior focus in the olfactory-midbrain areas; and that the negative reinforcement system might have a field in periventricular areas of the dorsal midbrain and medial hypothalamus which could

function by "inversely" modulating the olfactory-midbrain focus of positive reinforcement.

The view that anterior structures were relatively less important to self-stimulation has been tempered by experiments showing that the positively reinforced behavior could be abolished by temporary functional impairment of the whole cortex.

Functional impairment of the whole cerebral cortex, i.e., spreading depression Leão (1944) produced by the Burés method (Bures, 1959), caused complete and specific obstruction of the hypothalamic self-stimulation phenomenon (Burés et al., 1961). The Burés method involved production of spreading cortical depression in a chronic animal by application of KCl-soaked pledgets to cortex exposed through trephine openings. With bilateral applications of 22 percent KCl, repeating waves of spreading depression occurred, which precluded all food-directed behavior for as much as 4 hours (Burés, 1959).

Similar application of KCl in self-stimulation experiments caused immediate and complete cessation of self-stimulation behavior driven by lateral hypothalmic stimulation (Burés et al., 1961). During the same period, a large component of the escape behavior driven by dorsomedial tegmental stimmulation continued. Specifically, it appeared that an operant or learned component of the escape behavior disappeared with the self-stimulation, and that a reflex or unlearned component of the escape behavior survived. Rüdiger and Fifkova (1963) used this method to find whether self-stimulation, in the lateral hypothalamus was related to the cortex of the same or the opposite side. Their data showed that unilateral spreading depression on the same side caused severe impairment of self-stimulation and escape behavior produced by hypothalamic stimulation.

The study of Burés et al. (1961) presented an interesting account of neurophysiological correlates which may cast light on the mechanisms involved. Unit activity at the dorsomedial tegmental escape point was briefly augmented during the spreading depression period; unit activity at the hypothalamic self-stimulation point was greatly depressed. A corticoreticular inhibitory path which was physiologically defined in several studies (e.g., Adey, 1958; Hugelin and Bonvallet, 1957) would probably account for the great augmentation of unit responses at the dorsomedial tegmental escape point. No similar corticohypothalamic facilitatory path has been described, however, to account for the depression of unit activity in the lateral hypothalamic self-stimulation area. While the possibility of such a path should now be taken seriously, an alternative hypothesis is that the excessive activity at the dorsomedial tegmental escape point directly inhibited activity in the lateral hypothalamic self-stimulation area. This would accord well with the inhibitory effects of dorsomedial tegmental stimulation on hypothalamic self-stimulation (Olds and Olds, 1962) reported in the previous section.

The hypothesis of such an inhibitory relation would serve yet another explanatory function. It might be a means of rendering equivalent the reinforcing event following hypothalamic self-stimulation and that following the learned tegmental escape response. In each case, there would be augmented activity in the lateral hypothalamus as the reinforcing event; in the self-stimulation case it would result from direct stimulation, and in the tegmental case it would be a release or rebound from inhibition. From this theoretical basis, it has even been suggested that, possibly, the learned

component of the escape behavior was sustained by the same mechanisms as the self-stimulation, and, therefore, both would be expected to disappear together under spreading depression as the Burés et al. (Olds et al., 1961) data demonstrated.

This would also provide some explanation of the anomalous outcome of the interaction study (Olds and Olds, 1962) mentioned previously, in which the escape behavior was actually augmented by a background of rewarding stimulation in the lateral hyphthalamus. If the learned escape behavior, like the learned self-stimulation, were in fact sustained by lateral hypothalamic activity, then more activity in this region might be expected to result in more behavior.

Electrophysiological Ramifications of the Stimulation

To many electroencephalographers it seemed reasonable to expect that self-stimulation would be associated with abnormal and possibly pathological electrographic activity in the brain. The bases of this expectation were at least four-fold: (1) the frequent observation of automatic behaviors during mild epileptic seizures, seizures associated with clearly discernable, pathological signs in EEG; (2) the occurrence (albeit infrequently) of autogenic "petit mal" epilepsies in which the patient sought to initiate or augment his epileptic episodes by manipulation of visual input; (3) the belief stemming from several psychological theories that behavior should be reinforced positively by an abrupt modification or reduction in stimulus input as would occur if the patient were suddenly taken with the state of unconsciousness or reduced consciousness which appears to accompany epileptic seizures; (4) the obvious fact that abnormal electrical activity was induced in the brain each time an electric stimulus was applied by means of an implanted electrode.

It seemed reasonable, therefore, to find whether and in what way electrical epileptic and epileptic-like discharges might be involved in self-stimulation, and to find some answers to whether the automatic behavior or reduced "consciousness" of epilepsy might explain the reinforcement produced by brain stimulation.

Three kinds of epileptic-like electrical activity were considered likely: (1) after-discharges at the site of stimulation and/or at closely related points, (2) spreading after-discharges which are the electrographic sign of epilepsy, or (3) random epileptic "spiking," which is the EEG sign of a quiescent epileptic focus.

Well hidden in the Journal of the Experimental Analysis of Behavior is the outstanding electrophysiological contribution in this area by Porter and his associates (1958; 1959). These experiments used multiple electrodes implanted in monkeys and recorded from a variety of olfactory-cortical and olfactory-midbrain areas during self-stimulation tests. They found that each 0.5 second train of stimulation in a boundary region between the field and focus of reinforcement caused a very transient epileptic-like discharge in nearby structures of the field. In some cases there was just one discharge for each stimulation, but with stimulating electrodes in a different place (which also caused self-stimulation) there were after-discharges. In the case where there was just one discharge for each stimulation, self-stimula-

tion lasted only so long as these discharges were produced, suggesting that they were somehow involved in the reinforcing function. When self-stimulation was about to cease, the crucial discharges disappeared and new discharges appeared in a different part of the olfactory-cortical system. In the case where there were after-discharges, self-stimulation would cease during the period of the after-discharges and then recommence when these stopped.

With electrodes in one part of the olfactory-cortical system, self-stimulation occurred often in conjunction with seizure activity. In several cases, the animals continued to self-stimulate only so long as seizures were produced, and lost interest if seizure activity became "adapted out." With other electrodes, in the same structure, self-stimulation occurred at intensity levels well below seizure threshold levels.

With electrodes in a different olfactory-cortical structure, quite the opposite correlation appeared. Animals would self-stimulate only so long as the stimulus failed to induce seizures. After seizures appeared, the animals would not self-stimulate for long periods of time, often more than 24 hours.

In the case of posterior focus self-stimulation, where response rates were very high, the continuous stimulation prevented satisfactory recording. It appeared, however, that there were no after-discharges following stimulation in these areas.

In summary, posterior focus self-stimulation went too fast for recording; anterior self-stimulation yielded single epileptic-like discharges in nearby areas that appeared in some cases "necessary" to maintain self-stimulation, but in these cases there were no after-discharges; in other cases anterior self-stimulation yielded similar waves with after-discharges, and in this case, pauses occurred during the after-discharges. Olfactory-cortical self-stimulation in one structure yielded full-fledged seizures that appeared to be positively reinforcing because they were, in several cases. "necessary" to continued self-stimulation. Similar self-stimulation in a neighboring structure sometimes yielded seizures which appeared to be negatively reinforcing because they brought self-stimulation to an abrupt halt with no resumption after the seizure had subsided.

Interpreting their work, Porter el al. (1959) mentioned the "autogenic seizures" in some epileptic children (Bickford et al., 1953). In these cases, the patient appeared to start his own seizure by causing a strong-light flicker. In a few cases, this was related to verbal reports of pleasure. However, Porter and his associates also cited Williams (1956) to suggest that the emotional tone of the aura depended on the focus of the seizure. As their self-stimulation occurred, more often than not, without even recorded after-discharges, the seizure problem was probably not the most important aspect of their contribution. Rather, the single spike and slow-wave complex, which appeared essential to self-stimulation in certain cases, might have indicated a prototype or perhaps even an exaggeration of a necessary diffuse electrical event which might characterize the several areas in which crucial consequences occurred after reward-stimulation. This might, in the end, be most important as a way to identify areas for further and more detailed study of the physiological consequences of such stimulation.

Operant Conditioning of Unit Responses

One course which a more detailed study might take was indicated by the experiments on operant conditioning of single-unit responses (Olds, 1960c; Olds and Olds, 1961). These experiments, which have been underway for several years without yielding categorical results, were started to determine whether single-unit responses in the motor or other areas might be treated like peripheral responses in positive reinforcement tests. In the work already reported, a circuit was arranged to make a brief train of hypothalamic stimulation occur as a regular consequence of a given single-unit response in order to learn whether this would cause the response to increase in frequency and to occur eventually at a maximum rate.

Rats were prepared first with self-stimulation electrodes in olfactory-midbrain areas. Preliminary tests established that very high self-stimulation rates were achieved, and no tendency to escape from stimulation was present. Rats which failed to meet these requirements were eliminated. Each rat was then placed in a stereotaxic instrument under barbiturate anesthesia. A trepine opening, 3 mm. in diameter, was made in the skull; the dura was cut away and microelectrodes of 1 ua in diameter (Green, 1958; Hubel, 1957; Wolbarsht et al., 1960) were lowered into the brain.

As the animal, still in the stereotaxic instrument, recovered from the barbiturate anesthesia, it was given repeated doses of meprobamate or carisoprodol (Soma, Wallace Laboratories). Either dose was 80 mg/kg. The dosage was repeated whenever the animal showed any tendency to try to escape from the instrument. Previous tests had shown that an almost paralyzing dose of these drugs failed to block self-stimulation (Olds and Travis, 1959). From this point on, the electrode was positioned downward through the cortex, hippocampal formation, thalamus, and so forth, stopping whenever a clear spontaneous response appeared. Responses appeared as 200- to 500-μv negative spikes, lasting about 1 msec; they were amplified and displayed on a cathode ray oscilloscope.

Unit responses were not considered satisfactory for the experiments if their resting frequency was more than about 2 per second. Responses were preferred if their resting frequency was something less than 1 per second; when such a response was observed, a three-step experiment was performed.

First, after several minutes of waiting, a 30-sec record was made of the spontaneous rate of the unit response. Second, an elicitation (or pseudo-conditioning) test was made. A series of twenty $\frac{1}{2}$-sec trains of stimulation (sine wave 60 cycle per second, 50 μa) was introduced via the olfactory-midbrain electrodes at a repetition rate of about one every 2 seconds. In this first test, an explicit effort was made to stimulate only in the absence of single-unit responses. A second 30-sec record of activity was made immediately after the test. In the event of elicited effects, each stimulation produced a series of responses from the unit, and no further tests were made. The microelectrode was then advanced until a new unit response appeared; if elicited effects were not found, the experiment continued. Third, a reinforcement test was made. The experimenter waited for a single-unit response and, each time it appeared, immediately delivered a stimulus to the hypothalamus. When this was done by hand, it was usually applied after each appearance of the response, with a delay of less than $\frac{1}{2}$-sec (this was the experimenter's

response time).

In a successful positive-reinforcement test, the single-unit response rate was greatly augmented by this reinforcement procedure. The increased rate outlasted the procedure by a variable period of time. Immediately after this procedure, a third 30-sec record of the unit's activity was made. It was the comparison of the three 30-sec records that comprised the data.

With microelectrodes in neo-cortical areas, there were no successful positive-reinforcement tests by this simple method. With microelectrodes in olfactory-cortical areas and in some related subcortical structures, numerous successful positive-reinforcement tests were observed. These took three forms: (1) simple augmentation of the response rate of a sporadically firing unit; (2) conversion of a sporadic grouped response pattern to a pattern of continuous firing; and (3) elicitation of activity immediately after stimulation, but only when this was given as a reinforcement.

The most striking cases were of the second type. They were recorded mostly from structures of an olfactory-cortical circuit which appeared to be "seizure-prone" on other tests. In these cases, the unit was originally responding in a sporadic pattern with single responses or groups appearing at less than one per second. When introduced during silent periods, stimulation did not cause any elicited firing. Such a stimulation could be continued for periods of five minutes or more without materially augmenting response rates. Then, if the stimulation was withheld and delivered only after the appearance of a single or a grouped response, five to twenty reinforcements would often suffice to cause a sudden burst of activity; the unit would then respond continuously at rates as high as 30 per second. This burst would sometimes last for a period of only several minutes. The amplitude of the supposed unit response would often decrease in orderly fashion during this period. Then, the unit response would disappear for a period of some minutes, to return at the original amplitude and frequency. From this point on, however, the stimulus, even if presented during silent periods, would elicit a burst of responding. It was as if some irreversible change now linked this response to the area of stimulation.

In other cases, the repetitive activity did not decrease or disappear, but continued at a high level for long periods. In these cases, it appeared that the reinforcement procedure might have made a more or less lasting change in the spontaneous discharge of the unit in question.

The most questionable aspect of these data derived from the anesthesia used; stimulation of the olfactory-midbrain system almost definitely counteracted barbiturate and meprobamate states, and this could have accounted for augmentation in response rates produced by stimulation. It was also suggested that increments in blood pressure might easily be involved. The results were not regularly reproducible under drugs such as curare which temporarily paralyzed the animal. This was not surprising, as animals under pain or stress did not self-stimulate (Olds and Olds, 1962); and the paralyzed animal was always under stress. But the necessity for a pain-relieving agent, which had its effects reversed by stimulation, forced the experiment to rely heavily on the preliminary uncorrelated stimulus control. If the uncorrelated stimulus failed to augment unit responses but the correlated stimulus caused augmentation, then the result seemed clear. However, elicitation did sometimes occur, perhaps as frequently as reinforcement. Thus the possibility always re-

that in the reinforcing cases, elicitation tests were simply stopped too soon for the given levels of anesthesia. If elicitation tests could be made a second time after reinforcement tests, the difficulty would be circumvented. But it was usually impossible to reverse the procedure. This was not surprising; animals that learned and extinguished a lever response for brain shock reward returned to responding when given a free series of trains; after conditioning and extinction, the reinforcing stimulus often elicited the instrumental response. On the other hand, it made the proof of reinforcement, as distinct from elicitation, all the more difficult.

Four methods are being used presently to circumvent the problem. First is the search for anatomical distinctions; if it is possible to discover an easily repeatable arrangement of stimulating and recording electrodes, such that elicitation never occurs at all, and if reinforcement can be shown regularly with the same arrangement, then the demonstration will be definite. Second is the double-barreled recording of experimental and control units from the same general area at the same time; in this case, elicitation applies equally to both units, but reinforcement applies only in the correlated case. Third is the attempt to produce full reversal of the response pattern by means of an automatic stimulator, which, under reverse conditions, rewards the animal only after a period of no response. Fourth is the use of chronic implantation of microelectrodes to dispense with anesthesia and restraint.

That the experiment might have a good likelihood of eventually yielding a definite proof of operant conditioning of unit responses, and that it might be possible to reinforce unit responses in quite a wide brain area, was suggested by the relative case with which the same response could be recorded for very long periods of time (sometimes several days) if the reinforcement procedure was used. Under no stimulation or uncorrelated stimulation, responses regularly disappeared within the first hour.

Effects of Drugs on Electric Self-Stimulation

A series of pharmacological studies of self-stimulation has been undertaken to test the hypothesis that the suppression of self-stimulation may be a common property of chemicals that successfully control psychotic agitation. This view was derived partly from the satiation tests mentioned earlier (1958c), which indicated that animals with hypothalamic electrodes self-stimulated to exhaustion, responding for periods over 24 hours. This uncontrolled response made it appear that a positive feedback process was possibly involved, a process which grew to a maximum state and continued there instead of leveling off at an optimum state (negative feedback). Such a process would constitute a danger to the organism because it would trap the animal in a unidirectional behavior. This suggested an alternative to the popular notion that an excess of sympathetic activity might underlie psychotic agitation (Brodie and Shore, 1957). Many episodes of psychotic agitation might have quite a different etiology, namely, an excessive positive feedback process subserving positive reinforcement mechanisms. A corollary would be the hypothesis that chemicals which successfully control psychotic agitation would also suppress self-stimulation.

Preliminary reports (Olds, 1957; 1959c; Olds et al., 1956; 1957) indicated that reserpine and chlorpromazine, which have been useful in the control of psychotic agitation, suppressed self-stimulation, and that pentobarbital and meprobamate, which have little value in psychosis, did not. It was also indicated that reserpine and chlorpromazine seemed to have different effects on self-stimulation, depending on electrode sites (Olds et al., 1956; 1957). This led to the hope that there might be drugs specific to certain drive-reward systems in the brain, a hope not yet realized in experimentation.

Understanding of chlorpromazine action in rats was greatly advanced when it was compared with meprobamate, pentobarbital, and morphine in combination approach-escape tests which used rewarding and punishing electrodes in the same animal (Olds and Travis, 1960; Olds and Olds, 1964). Chlorpromazine halted self-stimulation behavior in 2-mg/kg doses that permitted escape behavior to continue. Pentobarbital and meprobamate had just the opposite effect, halting escape behavior in doses that allowed self-stimulation to continue; the doses were 20 and 80 mg/kg, respectively. Morphine fell in between, halting self-stimulation and escape behavior at the same 8-mg/kg dosage.

The appearance of selective action against positive reinforcement achieved with chlorpromazine in this experiment was superficially in conflict with other reports (Cook and Weidley, 1957; Gavlitchek, 1958) which suggested that the drug acted selectively against avoidance or defensive mechanisms. However, when the effects of chlorpromazine on the approach-escape test and on the avoidance and defensive reactions were viewed in more detail, the apparent conflict disappeared (Olds, 1962, in press, 1964; Stein, in press, 1964b). In all cases chlorpromazine acted selectively against the voluntary or anticipatory component of behavior. In almost all negative-reinforcement tests the animal could heed a warning signal and, by some preparatory response, avoid or diminish the negative reinforcement. It was avoidance behavior with this anticipatory character that disappeared under chlorpromazine. All self-stimulation behavior also had this anticipatory character, as the animal was never stimulated until after the response occurred; and all self-stimulation behavior disappeared under chlorpromazine.

In its action on avoidance and self-stimulation mechanisms, chlorpromazine had almost the same effects as spreading cortical depression (Burés et al., 1961; Olds, 1962) It terminated self-stimulation altogether, as well as the voluntary or learned component of the escape response. If the explanation proposed earlier for the action of spreading depression was valid, namely, that self-stimulation and the learned component of the tegmental escape response were both sustained by activity of the same lateral hypothalamic system, then the drug data suggest that chlorpromazine acted selectively to antagonize or raise the thresholds of this system.

Whether the selective action of chlorpromazine against the lateral hypothalamic system was related to its anti-psychotic properties could not be determined directly because knowledge of neural mechanism was too sparse. Indirect evidence, however, was drawn by correlating data on the two kinds of effects Bennett (1959) cited evidence supporting the view that prochlorperazine and triflupromazine were more efficacious than chlorpromazine against psychotic symptoms, and that promethazine and promazine were of questionable value in treating these symptoms. Chlorpromazine itself fell between these two extremes. It was interesting, therefore, that these phenothiazenes were

similarly arrayed in their antagonism to self-stimulation (Olds and Travis, unpublished observation). In these tests with rats, the 0.5- to 2.0-mg/kg dose range was used with all compounds. Promethazine augmented self-stimulation. Promazine had no efficacy at all. Chlorpromazine effectively antagonized self-stimulation at 2.0 mg/kg. Prochlorperazine and trifluoperazine (a triflupromazine-like compound) were extremely efficacious against the behavior even at 0.5 mg/kg.

A series of simple but ingenious tests by Stein and others made it quite clear the chlorpromazine and possibly other phenothiazenes acted specifically to counteract the lateral hypothalamic system by raising thresholds, and that some anti-depressant compounds had opposite effects, facilitating the same system by reducing thresholds. One method permitted the animal to indicate its own threshold (Stein and Ray, 1960). Each successive brain shock was reduced in intensity by a small step. There were 15 or 20 equal current steps between a moderately rewarding top value and zero. A second lever could be operated at any time to reset the current to the top step; but the animal had to take time off from self-stimulation to do this. The test animal operated the stimulation lever until the current was driven down to a nonrewarding (or less rewarding) level and then indicated this level by operating the reset. In this way the animal repeatedly indicated the "reset" stimulus level and thereby permitted a continuous recording of these "thresholds" over a period of time.

Chlorpromazine at the low dosage of 1.5 mg/kg in rat caused a distinct rise in thresholds with no cessation of responding. More active phenothiazines, proketazine, and trifluoperazine caused self-stimulation to cease in 0.6 mg/kg doses and therefore the effect of these on thresholds was not established (Stein, 1961). On the anti-depressant side (Stein, 1961; 1962c; in press, 1964a), amphetamine at 0.75 and 1 mg/kg caused a marked fall in thresholds, although it was sometimes not quite clear whether animals under amphetamine showed a willingness to respond without any reward at all. Other "psycho-stimulants," cocaine and caffeine, had effects similar to those of amphetamine, but the stimulant drugs, picrotoxin, strychnine, and nicotine did not fall in this category (Stein, 1962c). The barbiturates, pentobarbital at 10 mg/kg, and phenobarbital at 30 mg/kg, both yielded unquestionable facilitation of the self-stimulation response by causing a definite lowering of thresholds (Stein, 1961).

In a further study (Stein and Seifter, 1961b) involving concurrent self-stimulation at two rewarding electrode sites, Stein produced some confirmation of the finding that chlorpromazine raised self-stimulation thresholds and that amphetamine compounds caused them to fall. In concurrent two-pedal, two-electrode self-stimulation tests, electric current was set considerately above threshold in a non-preferred anterior hypothalamic location and just on the verge of threshold in a preferred posterior hypothalamic position. The difference between these two settings caused the animal to distribute responses evenly between the two levers. In this case any drug which merely activated or quieted without changing thresholds at the stimulation sites would have caused equal modification on both levers. But if a chemical specifically raised thresholds, it would cause a shift away from the borderline threshold electrode and if it specifically lowered threshold, it would cause a shift toward this same electrode which was preferred at suprathreshold values. In this situation, metamphetamine proved to have selective effect in lowering thresholds, i.e., sensitizing the reward system; and chlorpromazine had the opposite effect, raising thresholds or desensitizing the system.

In another study, Stein and Seifter (Stein, 1962b; Stein and Seifter, 1961a) analyzed the paradoxical drug of the phenathiazine family, imipramine, which appeared to counteract psychotic depression rather than psychotic agitation when tested clinically. In these studies a self-stimulating rat was tested first with the electric stimulus just above threshold levels. Both chlorpromazine and imipramine depressed responding. Then a second test was made with the electricity set below threshold; neither chlorpromazine nor imipramine was efficacious. But amphetamine applied during the subthreshold tests lowered thresholds and caused self-stimulation to occur. In cases where amphetamine induced responding, an injection of chlorpromazine antagonized the self-stimulation behavior but imipramine greatly facilitated it. The authors concluded that amphetamine acted centrally by mimicking the adrenergic catechol amines, which were thought to be the normal stimulators of the reward system. Chlorpromazine was thought to act centrally by blocking these same adrenergic mechanisms, and imipramine was said to be efficacious by favorably influencing adrenergic activity in the reward system.

The view that compounds might be selective antagonists or synergists of the reward system insofar as they had these same relation to adrenergic mechanisms was partly supported by other work comparing chlorpromazine with amphetamine compounds. Miller (1957b) used the ambivalent response mentioned earlier (Bower and Miller, 1958) to test chlorpromazine and methamphetamine for effects on rewards and escape behaviors. He tested with two pedals, one to turn on the ambivalent stimulus, the other to turn it off. Animals moved regularly back and forth turning the stimulus on and off. Methamphetamine at 2 mg/kg caused a slowing of this shuttling behavior, a decline which started 45 minutes after injection and lasted for more than 45 minutes. Chlorpromazine (4 mg/kg) caused a similar decline which started 15 minutes after injection and lasted more than 75 minutes. On the surface the two depressions looked similar. When the data were analyzed in terms of speed of the turn-on and turn-off behaviors, however, a radical difference was shown. Methamphetamine caused the turn-off response to slow with the turn-on response as fast as ever. Chlorpromazine caused great slowing in the turn-on response with the turn-off response still occurring quite rapidly. Thus methamphetamine selectively depressed the escape tendency. Chlorpromazine selectively depressed the reward behavior. A similar selective action for amphetamine (3 mg/kg) in rats was demonstrated in another study (Olds, 1959c). This showed that the slow self-stimulation produced with ambivalent electrodes could be transformed to very raped self-stimulation by an injection of amphetamine. A similar action was demonstrated for meprobamate (80 mg/kg).

In other experiments (Olds and Olds, 1964; Olds et al., 1964), the effects of these drugs were assessed "simultaneously" on two different behaviors evoked in the same animal. Two electrode pairs were implanted in all rats. In one experiment (Olds and Olds, 1964), there was a self-stimulation electrode in olfactory-midbrain pathways and an "escape" electrode in periventricular pathways of the midbrain. Self-stimulation and escape behaviors were tested during alternating 4-minute periods. The alternation was continued for several hours so that during the time course of a drug effect each behavior would be tested repeatedly. Chlorpromazine (1 to 2 mg/kg) caused large depletions of self-stimulation and somewhat milder depletions of escape behavior.' Meprobamate (60-100 mg/kg) caused similar reductions in escape behavior, but only very brief depressions of self-stimulation. LSD caused similar brief reductions in self-stimulation with no changes in escape behavior. D-Amphetamine (2-3 mg/kg) augmented some slow self-stimulation but slowed some very fast self-stimulation, and augmented operant escape behavior. In another ex-

periment, there was an escape electrode in periventricular pathways of the midbrain and another escape electrode in periventricular pathways of the thalamus. Escape behavior evoked by thalamic stimulation was regularly far more resistant to antagonistic effects of chlorpromazine and meprobamate than the same behavior evoked by stimulation of the midbrain.

LSD-25, the violently psychotomimetic compound which, like amphetamine, may be a monoamine-oxidase inhibitor and therefore might be expected to facilitate adrenergic mechanisms, caused a brief decline in self-stimulation when it was administered at 0.2 mg/kg (Olds, 1959c; Olds et al., 1957; Olds and Olds, 1964). Another similar compound is LSD's close relative, bromo-LSD (BOL), which has no psychotomimetic properties. Some researchers think that BOL is kept out of the brain by a "blood brain barrier." In self-stimulation tests (Olds, 1958f; Olds et al., 1957), it sometimes mimicked LSD's action, halting self-stimulation at some electrode sites (0.5 mg/kg), yet it failed to mimic LSD when probes were in other sites.

The effect of BOL may be related to that of serotonin, a close relative of the adrenergic catechol amines. Serotonin is also thought to have an excitatory or inhibitory influence of one sort or another on the transmitter action in the hypothalamus. It was implicated antagonistically in many of LSD's actions outside the CNS but it apparently does not cross easily from the blood into the brain. Some think it, too, is stopped by a "blood brain barrier." In self-stimulation tests, serotonin (0.9 mg/kg) had no effect of its own, but it counteracted the LSD effect with some electrode placements, which were precisely the sites not affected by BOL. One might guess that if the electrodes were planted in areas where some "barrier" prevented an action of BOL, then serotonin had caused that same barrier to prevent the LSD effect.

To summarize this early work on the pharmacology of self-stimulation, the most surprising outcome was the fact that the "new" tranquilizers including reserpins and several tranquilizing phenothiazenes such as chlorpromazine seemed to have a "specific" effect in countering self-stimulation whereas the older barbiturates, along with alcohol (unpublished observations) and meprobamate, could be built up to levels producing ataxia without impairing the self-stimulation behavior. On the other side of the same picture, new and old psychological energizers seemed to augment self-stimulation but the exact relations were unclear. Amphetamine and caffeine exhibited, in some experiments but not in others, a specifically synergistic interaction with self-stimulation. Imiprimine, the paradoxically activating member of the phenothiazene family, potentiated augmentations produced by amphetamine but inhibited when given alone. Irponiazid (Olds, 1959b; Olds and Olds, 1958), the first of the "new" antidepressants, also augmented self-stimulation in certain combinations with other drugs (Poschel and Ninteman, 1963; Stein, in press, 1964a)

While many drugs which acted specifically against noxious stimulation and escape behavior, such as the barbiturates, had mild to no effects against self-stimulation, it was also clear that many drugs which "specifically" antagonized self-stimulation also "specifically" antagonized aversive behavior when the problem was avoidance (Sidman, 1953; Cook and Weidley, 1957) rathern than escape. This led to a ressurection of the old surmise that some common mechanism of operant reinforcement might exist between positive and negatively motivated behaviors, provided an operant (nonreflex) component was involved (Olds and Olds, in press, 1964; Stein, in press, 1964b).

In a later series of studies, Stark and Boyd (1963) discovered that peripherally injected compounds which might be expected to augment central levels of acetylcholine had a detrimental effect on self-stimulation. Moreover, Poschel and Ninteman (1963) found that peripherally injected compounds which caused augmentation of central norephinephrine levels had the opposite effect. Stark and Boyd (1963) made intravenous applications of physostigmine (which is effective both peripherally and centrally) and of neostigmine (which is effective peripherally only) as a control. Both would be expected to augment acetylcholine levels by inhibiting cholinesterase. Applications of physostigmine caused self-stimulation to fall to chance levels; neostigmine had no effect. The view that central augmentation of acetylcholine was at the source of the effect was bolstered by the fact that the centrally acting acetylcholine-antagonist, atropine, countered the effect, whereas atropine's "peripheral-only" counterpart, methylatropine, failed to counteract the effect. These data created the strong impression that central acetylcholine was detrimental to self-stimulation. Poschel and Ninteman (1963) used alpha-methyl-meta-tyrosine (MMT), "a drug which releases brain norepinephrine and dopamine without significant effect on brain serotonin," together with a monoamineoxidase inhibitor (to prevent the liberated norepinephrine from being oxidized and secreted) The combination of the two (but neither separately) caused a great increment in self-stimulation. Similar effects were obtained when tetrabenzine (which releases norepinephrine and serotonin) was substituted for MMT. When these data on cholinergic (i.e., acetylcholine-related) and adrenergic (i.e., norepinephrine related) drugs were viewed in the context of the previously reported inhibition of self-stimulation by chlorpromazine (which is anti-adrenergic), and augmentation of self-stimulation by amphetamine and iproniazid, both of which are, in one way or another, adrenergic synergists, the strong impression was created that central adrenergics promoted and central cholinergics counteracted self-stimulation (cf. Carlton, 1963). The data from central application studies (Olds et al., in press, 1964) did not support this impression.

Self-Injection
Direct Chemical Stimulation

In view of the implication drawn from pharmacological studies that the olfactory-midbrain system might be positively sensitive to adrenergic stimulation and negatively sensitive to cholinergic applications, it was surprising that direct chemical stimulation studies gave evidence of exactly the opposite set of relationships (Olds, Yuwiler, Olds, and Yun, 1964). Chemicals in very small amounts were directly applied in the olfactory-midbrain pathway. Effects on operant behavior rates of the chronic animals were measured. The independent variable was the chemical microinjection which followed each response; the dependent variable was response rate. The volume of each microinjection was 3×10^{-6} ml; the pH was 7.2; all solutions were at the osmotic pressure of interstitial fluid. Self-stimulation was caused by cholinergic compounds and counteracted by adrenergic chemicals and by serotonin. The cholinergic compounds acetylcholine, carbamylcholine, and acetylcarnetine were used. The latter two might be expected to mimic the effects of acetylcholine but to be immune to rapid inactivation by the cholinesterase of the interstitial fluid of brain. Both of these compounds, but not acetylcholine, yielded dependable self-injection behavior. One may imagine that acetylcholine failed because it was rapidly inactivated.

Self-injection behavior was also produced by a variety of compounds (many

of them endogenous) which withdrew ionic calcium from interstitial fluid; it has long been known the nerves become spontaneously active in a calcium deficient fluid. Phosphate, citrate, pyrophosphate and other chemicals stimulated by combining with and therefore depleting ionic calcium. Stimulation by means of these "depletors" was counteracted when epinephrine, norepinephrine, or serotonin was mixed with the depletor solutions. Thus these amines all counteracted chemical self-stimulation.

Thus the picture produced by direct application of chemicals was one of stimulation of the olfactory-midbrain reward focus by means of cholinergic compounds and counteraction by means of adrenergic ones. Three alternatives present themselves to atone for the direct differences between the implications of the peripheral application studies and those of the central application findings. It might be that peripheral administration of pro-cholinergic compounds created central excesses and therefore reversed effects. Another possibility was that the centrally applied chemicals were effective on fibers whereas the peripherally applied chemicals were effective on synapses. The third possibility was that negative feedback system might exist in relation to sympathomimetic (adrenergic) and parasympathomimetic (cholinergic) neurohumors such that augmentation of either in the blood stream produced a counter-reaction in the hypothalamic, homeostatic control center. In any event these studies give clear evidence that the relatives of acetylcholine can be substituted for the electric stimulus in self-stimulation tests, and that chemical self-stimulation can be stopped by direct application of the symathomimetic amines. The finding is of particular interest because acetylcholine serves as the final mediator of peripheral parasympathetic adjustments, and the sympathathomimetic amines serve as final mediators of peripheral sympathetic responses. The possible connection of parasympathetic mechanisms and central positive reinforcement mechanisms is thereby sterythered.

A similar relation between a chemical with important effects outside the CNS and self-stimulation systems has recently come to light in experiments using a soluable testosterone compound. Testosterone-sulfate as used by Fisher (1956) to provoke self-stimulation behavior in much the same fashion as the cholinergic chemicals.

Speculations

Approach Reactions and Drives

A large system of the brain, phylogenetically derived from the olfactory apparatus and possibly still specialized to chemoreception, apparently functions primarily to mediate conservative* and appetitive reactions. The former were revealed by observation of autonomic responses produced by electric stimulation in these areas, the latter by observation of the instrumental or consummatory responses yielded by the same stimulation. Besides these elicited effects, stimulation of the same areas had, on random behavior, the effect of a primary-reward on random behavior, causing avid repetition of those response sequences which were followed sufficiently often by the brain stimulus. These primary rewarding effects were demonstrated in self-stimulation experiments.

*A conservative animal is saving his energy and hoarding food or storing up body fat or reproducing the species; rest, restitution, etc.

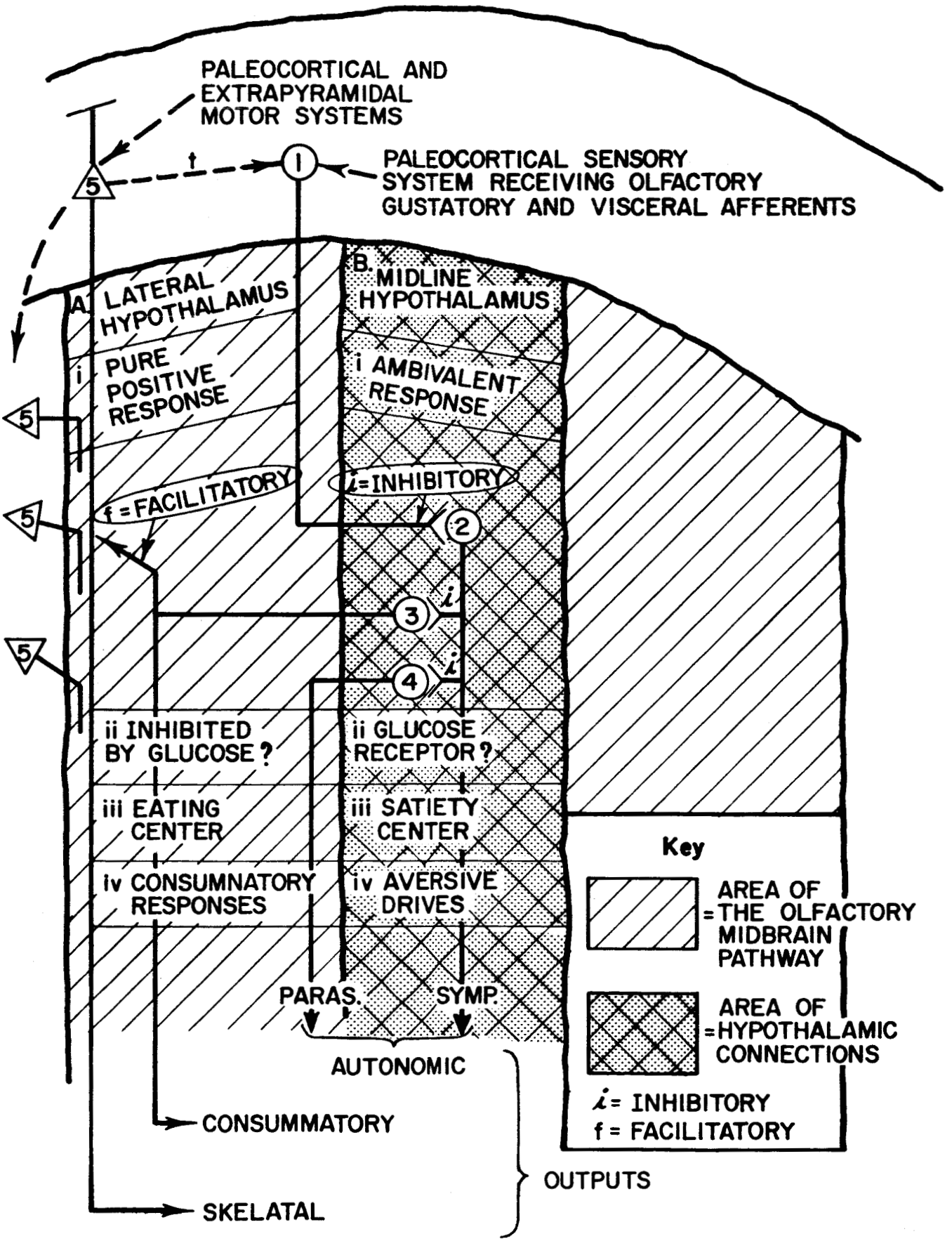

PALEOCORTICAL AND
EXTRAPYRAMIDAL
MOTOR SYSTEMS
PALEOCORTICAL SENSORY
SYSTEM RECEIVING OLFACTORY
GUSTATORY AND VISCERAL AFFERENTS
A. LATERAL HYPOTHALAMUS
i PURE POSITIVE RESPONSE
f = FACILITATORY
ii INHIBITED BY GLUCOSE ?
iii EATING CENTER
iv CONSUMNATORY RESPONSES
B. MIDLINE HYPOTHALAMUS
i AMBIVALENT RESPONSE
i = INHIBITORY
ii GLUCOSE RECEPTOR ?
iii SATIETY CENTER
iv AVERSIVE DRIVES
PARAS.
SYMP.
AUTONOMIC
CONSUMMATORY
SKELATAL
OUTPUTS
Key
AREA OF = THE OLFACTORY MIDBRAIN PATHWAY
AREA OF = HYPOTHALAMIC CONNECTIONS
i = INHIBITORY
f = FACILITATORY

Fig. 5

Experiments in which basic hunger or sex drives were manipulated during self-stimulation behavior suggested that the system was differentiated into subsystems on the basis of the different basic drives. Other data (Anand et al, 1961) suggested that the chemicals in the blood related to a particular basic drive constituted a major pathway of control over the correlated reward subsystem.

Another pathway of control was demonstrated by negative reinforcement experiments which indicated that certain aversive substrates had an inhibitory relation to the appetitive ones. The inhibitory relation of the negative feeding mechanism of the ventromedial hypothalamus to the "feeding center" of the lateral hypothalamus, and the apparent subservience of this negative mechanism to the glucose level (Anand et al., 1961) seemed to indicate that drive control over appetitive mechanisms might itself be mediated via negative areas which were inhibitory in relation to the appetitive system and negatively reinforcing in relation to behavior (see Fig. 5).

Figure 5. Possible organization of the reinforcement mechanism. Sensory fibers of paleocortex (1) might receive projections from olfactory, gustatory and visceral receptors and project inhibitory impulses onto drive centers in medial hypothalamus. Reduction of activity in these drive centers (2) would release lateral going fibers (3) and (4) from inhibition causing facilitation in the area of the olfactory midbrain pathways. Paleocortical and extrapyramidal motor fibers (5) originating in olfactory cortical systems might be interdigitated with the lateral going fibers (3) and receive a facilitatory output from those (3) fibers. It is possible that these motor systems might give direction to behavior; if so these would be the systems which received reinforcement from the lateral going (3) fibers. Stimulation of the drive centers of the medial hypothalamus (2) would yield both aversive consequences and inhibitory effects in relation to the lateral going systems (3) and (4). The suggestion that some part of this (2) area is also a glucose receptor shows that some of the aversive activity is thought to correlate with an excessively satiated rather than an excessively hungry state so far as the food system is concerned. It is interesting, but not quite anomalous that some of the medial hypothalamic aversive responses do seem to correlate with an excess of satiety (Hoebel & Teitelbaum 1962); psychology has tended to emphasize those aversive mechanisms associated instead with an excess

of hunger. My proposal indicated here (in iv) is that the aversive correlates of excess hunger might also be found in the medial hypothalamus in some as yet undiscovered centers and that the consummatory eating center of the lateral hypothalamus is mainly concerned with the positive reinforcement involved in eating. As far as the autonomic responses are concerned, sympathetic activity might be caused directly by activity in the medial drive centers (2) and parasympathetic activity (4) might be released from inhibition when this drive center activity subsided. In operant conditioning, the facilitatory relation (f) would directly increase the later response frequencies of the previously active motor elements (5), and the temporary connections (t) would cause a further indirect increment in response frequency.

A third line of control was suggested by the fact that the brain systems yielding self-stimulation were thought to be actual substrates of reward. If this were true, receptors in the viscera and periphery normally receptive to primary-reward stimuli would in one way or another send projections to these areas.

In any event, it was clear that stimulation of the same lateral area had two normally dissociated effects. On the one hand it had the effects of the primary drive itself, causing emission of drive-related instrumental and consummatory responses when suitable opportunities were offered. On the other hand it had the effect of the primary-reward related to that drive, causing repetition of the preceding behavior when it was used to reinforce operant responding. Therefore, the possibility that the electric stimulus constitutes a simple internal surrogate for either was unlikely. It seemed quite possible that the neural excitation attributable to primary drive and that attributable to primary reward were both projected to the same area with subtle differences in function, and that the electric stimulus, being something of a bludgeon, had the effect of both at the same time.

One was tempted to speculate that drive would ordinarily lower the thresholds of instrumental and consummatory responses related to the area but cause actual discharge only in autonomic efferents. Primary rewarding stimuli, finding the thresholds lowered, would then cause discharges in the efferents which controlled consummatory responses and by this same action cause some neural substrate of the preceding instrumental response to become related to this particular drive-reward focus.

These relations are schematized in Fig. 5. Drive in this diagram influences the system when low glucose levels cause a decline in the activity of the inhibitory glucose receptor. By suspending inhibition, this causes immediate discharge in autonomic effectors and lowered thresholds in the other neurones of the lateral system. Olfactory or visceral afferents then cause discharge in the other neurones, thereby causing consummatory responses and somehow tying the preceding skeletal response into this drive system. As for the pathway of control of olfactory or visceral afferents, the guess por-

trayed in Fig. 5 is that they further inhibit the medial inhibitory system, thereby yielding spontaneous activity even in the less active cells of the lateral system.

Mechanisms of Reward

The basic question posed by these findings and speculations is this: what does it mean for the substrate of some instrumental response to become related to a particular drive-reward focus? One can only speculate. From the experimental analysis of behavior, some aspects of the meaning may be guessed, namely, (1) that the threshold is generally lowered by the relationship so the response might be more frequent in the future, and (2) that its threshold is also brought into some relation with the correlated drive so that the active drive may cause even further lowering of its threshold. Possibly also, a third consequence is involved, (3) that the neural substrate of the behavior represents a new pathway of control over the focus in question so that stimuli tending to arouse the behavioral substrate will also have some tendency to arouse the drive in the future (cf. Olds, 1959a).

For further hints about the mechanism, we may turn our attention briefly to the nature of the neuroanatomical substrate of the drive-reward focus. We can never be sure which of the structures near an electrode tip is yielding a particular effect. However, if a large number of brain points are tested, and those yielding an effect follow a patterned course through the brain, it becomes a matter of ever-increasing likelihood that any anatomical structure following a similar course is importantly related to that effect. On the basis of such reasoning, it may be guessed that the main substrate of reward is a set of interstitial elements which forms a system in the olfactory-midbrain and olfactory-cortical areas. Increased activity in these elements appears to be the final mediator of the reinforcing effect. An increment of excitation of these elements following closely after a randomly emitted operant response may cause the later repetition of the operant. On the basis of evidence from pathological tissue, Papez (1958) speculated that these elements were granule cells acting as chemoeffectors, that is, neurosecretors, which might accomplish their reinforcing effect by facilitating excitation in their longer-axoned neighbors, or in passing fibers whose cell bodies might be at some distance.

From the self-injection experiments it might be guessed that these interstitial elements do not have excitatory afferents but instead have high spontaneous activity rates controlled on the one hand by local ionic balances and on the other by the inhibitory input from negative areas. If this were so, the consequences of electric stimulation at positive and negative reinforcing centers would be explained. For insofar as increments in activity of these elements caused positive reinforcement in ongoing behavior, it is clear that stimulation of these cells directly would yield positive reinforcement at the onset of the stimulus, while stimulation of the inhibitory afferents would yield similar reinforcement upon termination of the stimulus.

If the interstitial elements of the medial forebrain bundle were spontaneously active and controlled by inhibition only, and if they formed a substrate of reward, the interesting possibility would arise that primary rewards might have their effect on the system by a process of double inhibition (see Fig. 6). They might be projected to the positively reinforcing ol-

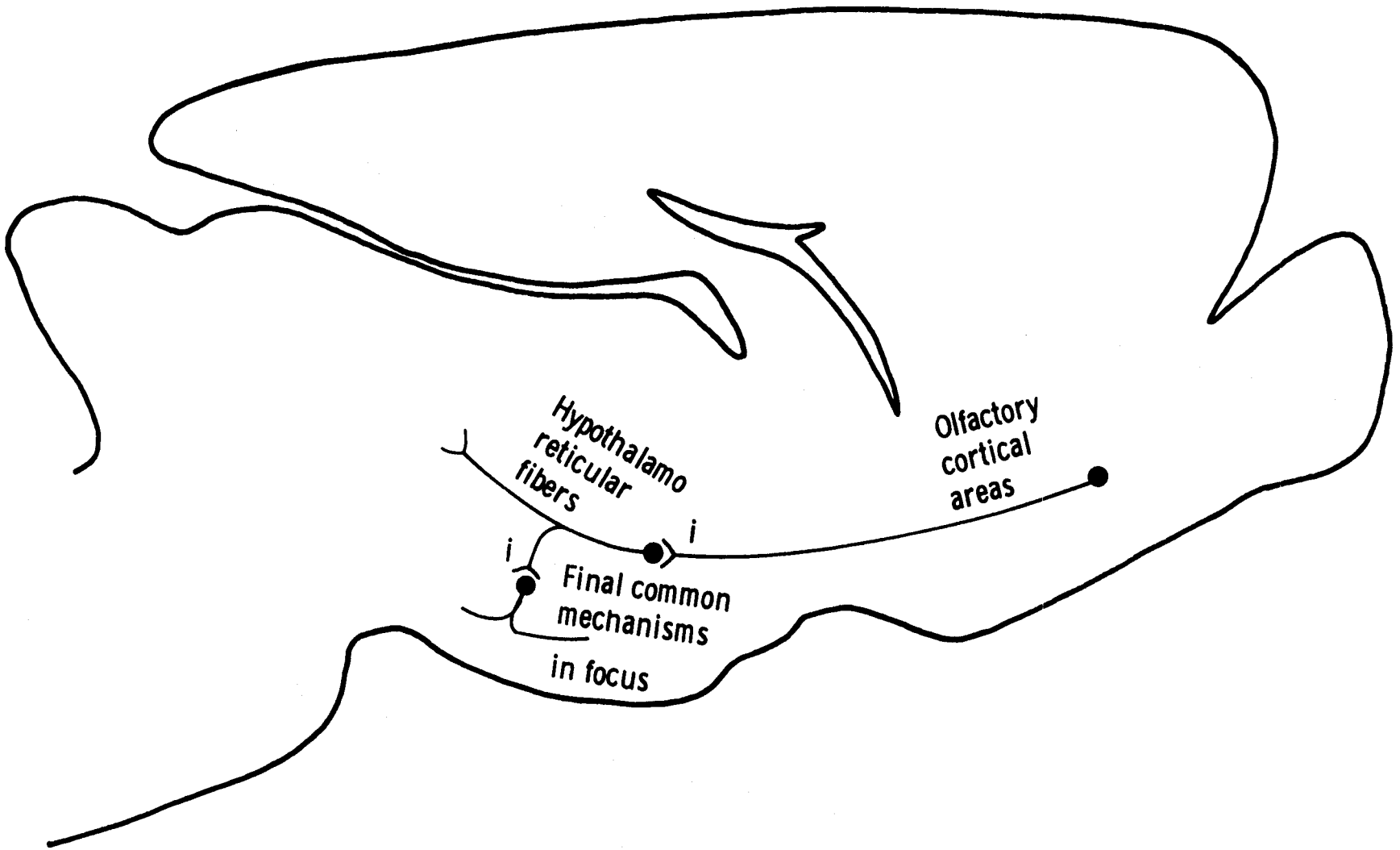

Hypothalamo
reticular
fibers
Olfactory
cortical
areas
i
i
Final common
mechanisms
in focus

Fig. 6

Figure 6. A possible double inhibitory relation linking olfactory-cortical reinforcement centers to a focus of reinforcement. i = inhibitory synapse.

factory-cortical areas such as the entorhinal area, which, from the work of Adey (1958) and Fonberg and Delgado (1961), might be thought to inhibit the inhibitors of the interstitial elements. Certainly, clear evidence of such a pathway exists: (1) electrical stimulation of the entorhinal area caused moderate reinforcement, as with a reward stimulus from the environment (Brady, 1961); (2) stimulation of the entorhinal area also caused inhibition of unit responses in the dorsomedial midbrain (Adey, 1958); (3) stimulation of the dorsomedial midbrain caused negative reinforcement (Olds and Peretz, 1960); and (4) stimulation of this same midbrain area caused inhibition of the lateral hypothalamic self-stimulation response (Olds and Olds, 1962).

Summary

In summarizing such material as this, it does no harm to make a clear separation between the established facts and the tempting speculations. The speculations have been presented; the facts are listed below, grouped according to the major parts of this review.

1. Electrical stimulation in a very broad set of brain areas yielded effects on behavior tantamount to those of primary reward. The areas involved were largely in the hypothalamus and the rhinencephalon.

2. With the current correctly adjusted and the electrodes correctly placed, it was possible to generate more motive force with this type of reward than with any other reward used in animal experimentation. With the current set lower, or the electrodes placed differently, far milder effects were achieved, effects comparable in every way with conventional rewards. With electrodes implanted in the olfactory-cortical areas, satiation occurred so that animals self-stimulated daily for certain, but not indefinite, periods of time. With some hypothalamic electrode placements, there was no satiation so that animals self-stimulated to the point of exhaustion.

3. With electrodes in some places, the tendency to self-stimulate was a monotonic function of the electric current level: in these cases, the tendency to approach became more and more augmented as the current was raised; tests were made with the current at more than 20 times the threshold settings. With electrodes in other places, the self-stimulation rate rose with early current increases and declined with later increases.

4. The self-stimulation phenomenon was regularly provoked by stimulation of approximately the same areas as those previously implicated in studies of various basic drives. Self-stimulation via differently placed electrodes was sensitive to manipulation of different basic drives: furthermore, these self-stimulation electrodes often yielded the correlated consummatory responses

if the stimulus was delivered by the experimenter and the response opportunity existed. Conversely, electrodes yielding consummatory responses often yielded self-stimulation.

5. Besides the areas where stimulation yielded positively rewarding effects, there were other areas in the brain where stimulation yielded negatively reinforcing primary-punishing effects, and there was a third and perhaps most numerous set of placements where stimulation seemed to yield both effects about equally. MFB points in the olfactory-cortical and olfactory-midbrain areas were especially apt to yield pure positive reinforcement; dorsal thalamic and midbrain points were especially apt to yield pure negative reinforcement; and points in middle hypothalamus regularly yielded both effects.

There was interaction between some negatively reinforcing areas and some positively reinforcing areas in olfactory-midbrain pathways such that stimulation of the negative area was antagonistic to the self-stimulation behavior produced by stimulation in the positive area, but stimulation of the same positive area was synergistic to the escape behavior produced by stimulation in the negative area. In other cases stimulation of olfactory-cortical positive areas countered the escape behavior produced by stimulation in the negative area.

6. Lesions in several cortical portions of the positive-reinforcement system did not prevent self-stimulation via midbrain electrodes. Spreading depression in the neocortex of the rat, on the other hand, caused cessation of all self-stimulation and of the operant component of negatively reinforced behavior, while reflex escape behavior survived. The same spreading depression caused vast augmentation in unit firing at the midbrain escape point and vast depression of unit firing at the lateral hypothalamic self-stimulation point.

Electroencephalographic studies showed that self-stimulation in the cortical part of the medial forebrain bundle was often accompanied by after-discharges in the septal area and the hypothalamus. It was not clear whether similar after-discharges occurred with other self-stimulation electrodes, nor was it clear whether they were actually involved in the reinforcing process.

With hippocampal self-stimulation, seizures evoked by the self-stimulation electrode appeared synergistic to the positive reinforcing process. With amygdaloid self-stimulation, seizures evoked by the self-stimulation electrode appeared antagonistic to the positive reinforcing process. It seemed clear that seizures were in no way prerequisite to self-stimulation.

Microelectrode studies indicated that olfactory-cortical single-unit responses, which were used experimentally to trigger rewarding hypothalamic stimulation, often became vastly augmented in spontaneous discharge rate. No similar modification in the rate of the triggering unit was produced when neocortical units were used to trigger the same stimulus.

Autonomic responses were regularly evoked by stimulation of the areas involved in self-stimulation, but it was not definite that these were primarily parasympathetic, as was originally thought.

7. The self-stimulation animal was sufficiently alert during periods of stimulation to discriminate between two different tones. However, uncontingent application of the electrical stimulus during the learning of a discrimination problem caused drastic impairment. Similar uncontingent application of a stimulus caused the dominant male of a monkey colony to loose its position.

8. Tranquilizers of the phenothiazene group regularly abolished self-stimulation behavior and the voluntary component of escape behavior, permitting reflex escape behavior to continue. These effects appeared to be achieved by a direct or mediated action of the drugs on hypothalamic thresholds. Barbiturates and meprobamate did not have similar effects. Activators of the amphetamine group appeared to have the opposite effect, augmenting self-stimulation by lowering hypothalamic thresholds.

Preliminary tests utilizing intravenous or intraperitoneal application of synergists and antagonists of acetylcholine and norepinephrine suggested that the self-stimulation system might be positively sensitive to norepinephrine and negatively sensitive to acetylcholine.

Microinjection studies showed just the opposite set of relationships. Acetylcholine-like compounds and compounds which caused a loss of local ionic calcium and tectosterone sulfate aroused the reinforcement mechanism when applied directly in the olfactory-midbrain pathways. These drugs could substitute for electricity in self-stimulation tests. Such chemical stimulation was counteracted by addition of epinephrine, norepinephrine, or serotonin to the chemical stimulator solutions.

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