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THE HIPPOCAMPUS AND BEHAVIOR[1]

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The literature on the behavioral effects of hippocampal lesions is reviewed and it is concluded that a lesion produces a unitary deficit. On a purely descriptive level this deficit consists of an ability to withhold a prepotent response, whether learned or unlearned. Many hypotheses about hippocampal function are shown to be inconsistent with the data or otherwise inadequate. 4 ideas appear to be generally supported by the results in the literature, and these essentially represent slightly divergent views about possible causes for the deficit above. In 3 of these, the hippocampus is postulated to have an inhibitory function, whether Pavlovian, S-R bond suppression, or inhibition of attention and/or stimulus input. In the 4th idea, the hippocampus is postulated to play a crucial role in a working memory mechanism.

Within the last 5 years more studies of the effects of hippocampal lesions on behavior have been published than in all previous years combined. Despite this proliferation of specific knowledge, no comparable advance has been made in a general understanding of hippocampal function. Particularly to the nonspecialist in this area, many of the latest findings appear to be at best confusing and at worst contradictory. It is the purpose of this paper to demonstrate that many of the apparent contradictions are only superficial and are due in large part to differences in techniques. For example, the size of a "hippocampal lesion" may vary from a tiny spot of destruction to complete removal of this very large structure. Tasks with the same title have often included procedural differences so great that they were probably measuring different things. The term "avoidance task," for example, has been used to describe three profoundly different problems. In the following analysis it is shown that when these factors are taken into account most of the contradictions vanish and are replaced by a high degree of consistency. The results are shown to fall into an easily recognizable pattern which implies a unitary function of the hippocampus in the determination of behavior.

Since this review is primarily concerned with the hippocampal-lesion literature, some of the more relevant findings in the fields of neuroanatomy and electrophysiology are summarized briefly. Excellent detailed reviews of these topics already exist (e.g., Cajal, 1955; Green, 1964; Kappers, Huber, & Crosby, 1936; Stumpf, 1965) and in most cases material available from these sources or any introductory text is not cited. As far as possible, review articles are cited.

Anatomy and Physiology

The hippocampus has a number of special or unique features which have attracted the interest of investigators in a wide variety of disciplines. It is an extremely active structure, both biochemically and electrically, and it is ultrasensitive to many factors which influence brain functioning in general, such as anoxia or the presence of toxic substances. The hippocampus contains a type of cell found nowhere else in the nervous system, the double pyramid, and its motor and sensory cells are neatly segregated in layers, much to the convenience of investigators of single-unit activity. Hippocampal electrical activity has aroused great interest. The structure is highly prone to electrical seizures, and one of its characteristic rhythms (the theta rhythm, 4 to 7 cps) compares favorably to alpha in the amount of study which has been invested in it.

Another feature of the hippocampus is its extreme size. In some mammals it occupies up to one-quarter of the forebrain. One would intuitively suspect that sheer size should be

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n indicator of importance. Although the elative size of the hippocampus, compared o the neocortex, diminishes in the higher nimals, the absolute size does not. The number of fibers contained in one of its major paths of outflow, the fornix, reaches a climax in man. This number could conceivably be used as an index of evolution in much the same way that the fiber count in the pyramidal tract is sometimes used, and with no less validity. In terms of prolongation of cell division processes, some parts of the hippocampus could be considered to be as highly evolved as the outermost layer of the neocortex, because cell division in the entire structure is not completed until the twentieth day after birth in the mouse (Angevine, 1965). Thus, despite the fact that the hippocampus is a phylogenetically ancient structure, dating back to at least the mesozoic era, it has probably continued to evolve and does not appear to be in the process of becoming vestigial.

The hippocampus is usually classified as part of the limbic system, a collection of brain structures united largely by the fact that they appear phylogenetically earlier than the neocortex and lack the six-layered construction of the latter. The number of layers contained in a brain structure should not be used as the basis of a value judgment, however, as there is no known relation between the number of layers and efficiency or importance of function. While authors disagree on which structures should be included in the limbic system, the amygdala, septal region, cingulate gyrus, entorhinal cortex, and hippocampus are always included as major parts. The use of the term "system" would appear to imply that these areas cooperate in a common function, but no such common function has yet been found. Lesions of these separate areas are known to produce markedly different symptoms, and it would perhaps be more fruitful to consider each item in the above list as a separate entity pending further evidence. In the present analysis, the hippocampus is assumed to be a functional

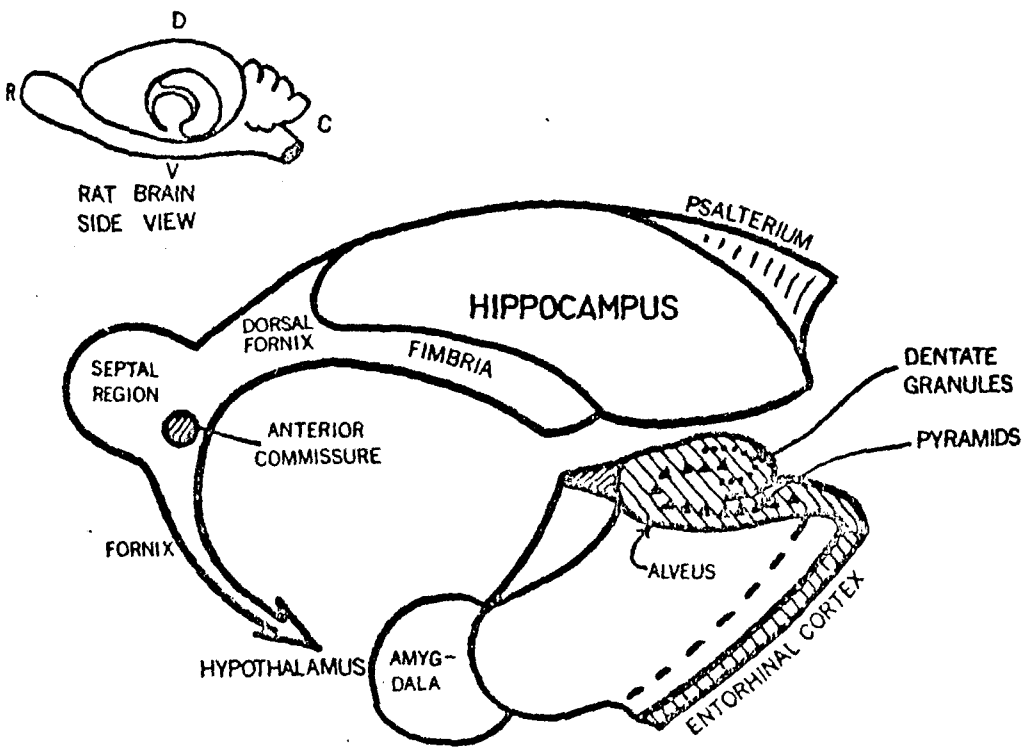

FIG. 1. Schematic diagram of side view of the hippocampus in the rat, with section through middle portion.

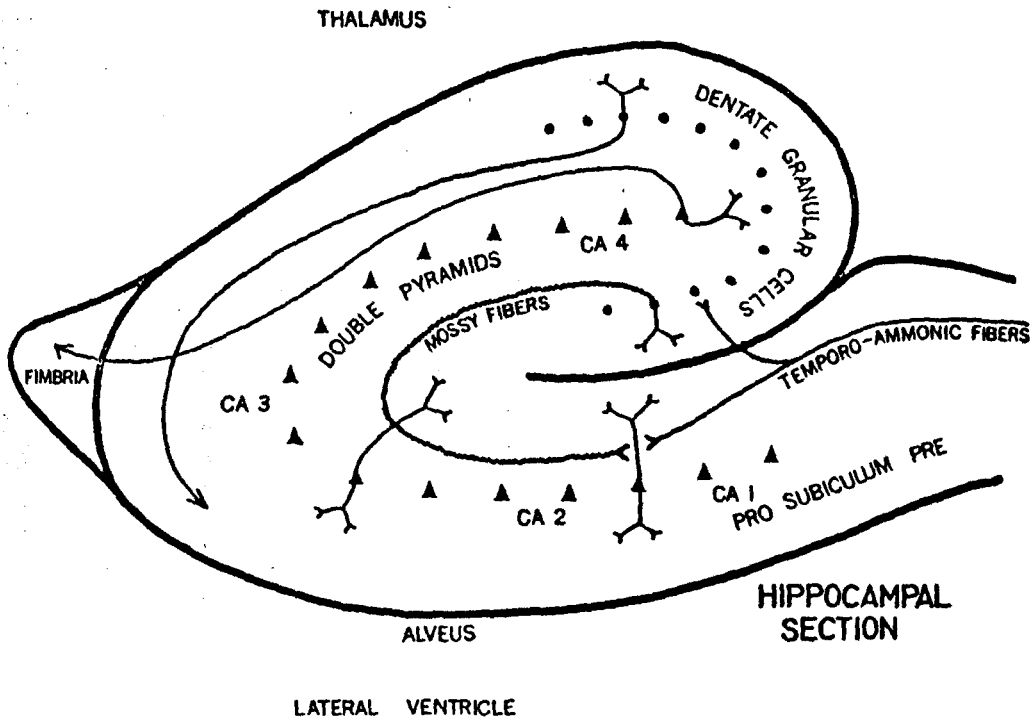

FIG. 2. Close-up of section in Figure 1.

entity until proven otherwise, because the studies in the literature almost invariably involve lesions of more than one anatomical subdivision of his structure and most do not involve damage to other limbic-system areas.

As can be seen in Figures 1 and 2, the entire hippocampal formation includes entorhinal cortex, subiculum, and pyramidal layers merging into each other with no clear boundaries. The tip of the sheet of pyramids is capped with a roll of sensory-type cells known as the dentate gyrus. While these areas can be further subdivided anatomically, this is irrelevant for present purposes. In the remainder of this paper, the term "hippocampus" refers to a combination of pyramidal and dentate areas which makes up the bulk of the horn-like structure shown in Figure 1 (Ammon's horn). The entorhinal cortex and subiculum are not included in this term. The terms "hippocampectomized," "hippocampally ablated," and "hippocampally lesioned" refer to bilateral damage to Ammon's horn, either in whole or in part. Studies in which other limbic areas, such as the amygdala, have been included in the lesion are not considered unless especially pertinent, as in most cases the results might be due to involvement of the other region.

Many of the connections between the hippocampus and the rest of the brain must be inferred from electrophysiological evidence and have not yet been fully confirmed anatomically. Two of the major connections are, however, so obvious to inspection that there has perhaps been a tendency to ignore other possibilities. The fornix is a huge fiber bundle which exits from the hippocampus and curves ventrally and caudally into the posterior hypothalamus near the mammillary bodies. Some of these fibers terminate in the septal region, which also contributes some fibers to the fornix. Fornix fibers also terminate throughout the hypothalamus. In some species fornix fibers continue into midbrain reticular areas, while in others this pathway continues after a synapse. In addition, there is a pathway back to the hippocampus from the mammillary bodies which takes a circuitous route through the ventral anterior

nucleus of the thalamus, cingulate gyrus, and back to the hippocampus by way of the entorhinal cortex (Papez, 1937). While there is no doubt that the separate connections between structures in this pathway (known as Papez' circuit) do exist, there is no conclusive evidence indicating that this circuit actually constitutes a functional pathway significantly involved in the determination of behavior.

A major source of hippocampal input is the temporoammonic tract, which consists of discrete fiber bundles which enter the hippocampus from the entorhinal cortex. Thus, the hippocampus has classically been considered to be a structure which receives its input through the subiculum and discharges from the fornix. Within the last decade, however, the reverse of this direction has been given increasing attention. It has now been established that the hippocampal theta rhythm is paced by rhythmically firing cells located in the septal region which send their axons into the dorsal fornix on their path to the hippocampus. Thus, the fornix contains hippocampal afferents as well as efferents. Other investigators have studied connections between hippocampus and entorhinal cortex in which impulses are conducted in a direction opposite to that of the temporoammonic tracts. Adey, Merrillees, and Sunderland (1956) found that in the marsupial phalanger, a pathway extends from entorhinal cortex to midbrain tegmentum via the stria medullaris. Adey, Sunderland, and Dunlop (1957) reported that fornix or hippocampal electrical stimulation resulted in readily detectable evoked responses in the entorhinal cortex while only small and irregular evoked potentials could be found in the fornix after electrical stimulation of the entorhinal cortex. Stimulation of either middle hippocampus or entorhinal cortex produced evoked potentials in midbrain reticular areas, with the latency being shorter in the latter case, as would be expected for this "reverse" pathway. Votaw (1959, 1960) has also demonstrated the existence of septal-hippocampal-entorhinal conduction in his investigations of the rather peculiar response which can be elicited with electrical stimulation of either sepal region or hippocampus. This response resembles an extreme withdrawal or startle reflex; and if it is produced by septal stimulation, it can be abolished by fornix section. If it is produced by hippocampal stimulation, it is not affected by fornix section and is abolished only by a section between hippocampus and entorhinal cortex. While the results of these studies demonstrate that conduction takes place in both directions along the septal-hippocampal-entorhinal axis and that an a priori designation of one of these as the more important would be ill-founded, they also suggest something further. According to these findings, there is a possibility that the hippocampus could still function, in part, after complete section of the fornix or after a rostrally placed lesion of small extent. The reason is that after this section the hippocampus retains a source of massive input as well as an apparently powerful output system. The integrative functions of the hippocampus, as far as these are determined by cellular interconnections, would also remain intact. For this reason any assumption that extremely rostral hippocampal lesions or fornix sections are equivalent to total removal of the hippocampus must be guarded. Behavioral evidence bearing on this point is discussed later.

The next matter to be considered is the nature or significance of these input and output pathways. Although the septal region appears to be of crucial importance in the pacing of theta waves, the septal region also receives a theta-like input from brain stem reticular areas. The septal region has been considered to be a nonspecific or convergent area for stimulation in a variety of sensory input systems, including the visceral (see Votaw, 1960). Both the source of septal input and the relatively few cells involved in theta pacing suggest that little specific sensory information could be conveyed over this channel. Instead, it would appear more likely that this pathway provides information of an emotional, motivational, or arousal nature. Green and Arduini (1954) and many others have found hippocampal theta activity in response to stimulation in a variety of systems, but the stimuli were typically of an extremely arousing or even noxious type. These studies do not demonstrate, however, that this pathway exists for the express

purpose of producing theta rhythms. The question that one might ask is what this pathway is doing when theta is not produced. The fact is that animals are continuously subjected to stimulation and yet theta waves are more often than not absent from hippocampal records. The pacing of theta waves may be only a special (and relatively rare) function of this pathway in response to intense stimuli. Since theta rhythms are usually found in conjunction with neocortical desynchrony, and since the latter is often an indicator of behavioral arousal, it has often been assumed that theta rhythm indicates arousal or intense functioning of the hippocampus. There is, however, no direct proof for this contention, and theta rhythm may actually indicate hippocampal inactivity, as is discussed in detail later. It challenges belief that a brain structure could generate very high amplitude sine-like waves and yet be functioning in any discrete fashion.

In addition to the eliciting of theta rhythms, stimulation of various sensory systems has also been found to result in evoked potentials in the hippocampus (Cragg, 1960). The pathways involved in these evoked potentials are not necessarily the same as those involved in the pacing of theta waves. Cragg (1961) found evidence that impulses generated in the olfactory bulbs reach the hippocampus via entorhinal and subicular regions. He found that lesions in the areas where olfactory bulb fibers terminate (prepyriform, periamygdaloid, and olfactory tubercular areas) resulted in a degenerating pathway entering the hippocampus by the route just mentioned. Wendt and Albe-Fessard (1962) found a somewhat analogous situation in the case of amygdaloid input from the somatosensory system, which was relayed after a synapse in a neocortical secondary sensory projection area. Niemer, Goodfellow, and Speaker (1963) also found that stimulation almost anywhere in the neocortex, including "association" areas, results in evoked potentials in the hippocampus, although the pathway was not discovered. These findings are of theoretical importance because they suggest that the limbic system receives information of a very high order, which is necessary if these areas function in the control of the higher mental or behavioral processes. In the case of the hippocampus, these findings suggest that the hippocampus receives two different types of input over two different pathways. The first, through the septal region, might indicate the motivational state of the animal or the importance of a stimulus. The second, relayed from the higher neocortical analyzing areas through the subiculum, might contain input of a much higher informational content which has been "predigested." One possible function for the two hypothetical types of input is that the first has a selective function while the second provides material to be selected from. This leads to the question of what the selection is for, and one possible answer is a selection for attention. The brain must have a mechanism which sorts input for attention or relevance, and this might involve the hippocampus. If the hippocampus is actually involved in a selective function of this type, it must be a negative or exclusive function, as is discussed after the lesion data have been presented.

The precise nature of hippocampal output is presently unknown. As was mentioned earlier, Votaw (1959) has found what resembles an extreme withdrawal response to occur with electrical stimulation of the hippocampus. This is a rather gross movement, however, and does not suggest that the hippocampus is involved significantly in motor behavior because nothing resembling a motor homunculus was found and no discrete movements were discovered. The powerful connection between hippocampus and hypothalamus via the fornix does suggest a possible control over autonomic and/or emotional processes, but lesion studies do not support this idea. This apparent paradox may be eventually solved when autonomic activity is disentangled from its emotionality connotations. Already there is much evidence accumulating that the autonomic nervous system plays a large part in perceptual and attentional factors only peripherally related to the emotions (e.g., Lacey, Kagan, Lacey, & Moss, 1963). An additional clue as to the meaning of a hippocampal-hypothalamic connection may have been provided by Feldman's (1962) report that sensory or lemniscal

stimulation leads to the production of evoked potentials in the lateral posterior hypothalamus and that stimulation of the hippocampus inhibits these potentials. Thus, the present fragmentary knowledge of hippocampal input and output suggests that this structure may be involved in the sorting, selecting, or modulating of sensory input.

Two types of electrical activity of the hippocampus have intrigued investigators. One of these is seizure, which may actually be induced by the amygdala in some cases, but can be produced even by a slight mechanical pressure on the exposed hippocampus. These seizures often precede and accompany epileptic attacks or automatisms, and when induced in animals tend to abolish learned behavior for the duration of the seizure and afterdischarge (Flynn, MacLean, & Kim, 1961). While there can be little doubt that these seizures prevent the hippocampus from functioning normally, they may have a positive as well as a negative effect, since behavior during hippocampal seizures does not resemble that observed after removal of the hippocampus. While it is probably valid to assume that normal hippocampal function is lost for a least the duration of the afterdischarge, it is probably not valid to assume that the hippocampus is functionally ablated during this period and that the behavior observed during the seizure is entirely attributable to loss of function.

The second type of intensively investigated hippocampal electrical activity is the theta rhythm, discussed earlier. It would be a mistake to equate theta activity with hippocampal functioning, not only for the reasons mentioned earlier, but also because the hippocampal electrical record rarely contains pure theta waves even in those species in which theta rhythms are easiest to detect. Hippocampal electrical activity more often resembles the blade of an old-fashioned crosscut saw, with the complex wave often containing a component of theta frequency (4 to 7 cps), although this is not considered to be true theta of the same type due to septal pacing. The theta-like component of the "normal" hippocampal record may be due to recurrent inhibitory connections between pyramidal cells (Spencer & Kandel, 1961), and the pure theta wave may be an enhancement of activity of a cyclic nature in these loops (see Stumpf, 1965). Theta rhythms are relatively easy to find in some animals (such as the rabbit), more difficult to detect in the cat, rarely seen in the monkey, and possibly absent altogether in man. This does not necessarily imply that the function (or lack of it) signified by theta activity is absent in the higher animals. Instead, it may merely mean that the electrical manifestation of this function is different in different animals, as is the size or position of the hippocampus. In the presumed course of evolution from marsupial to man, the hippocampus is pushed from its original medial dorsal position backwards and downwards until it finally rests in the depths of the temporal lobe in man. This migration is probably forced by the enormous expansion of the corpus callosum, which is part of the anterior commissure in marsupials, and it results in the fornix becoming greatly elongated. These changes might well have resulted in the production of different types of electrical activity by basically similar systems.

Several attempts have been made to relate the occurrence of theta rhythms to behavioral variables, but there is some disagreement even about basic findings. Grastyan, Lissak, Madarasz, and Donhoffer (1959) found theta to occur prominently during orientation to a familiar stimulus and in beginning stages of learning or extinction, but not the later stages. Adey, Dunlop, and Hendrix (1960) did not find a close relationship between theta and orienting, and reported that theta rhythms accompanied a discrimination response in the cat even after prolonged learning. These differences may be due at least in part to the very different tasks used by the two groups. Grastyan et al. (1959) employed a two-way active shock-avoidance task, while Adey et al. (1960) used a food-reinforced two-choice discrimination problem. Both groups used cats as subjects. It is of some interest that both found prominent theta rhythms during the learning or performance of tasks which the lesion literature indicates do not require hippocampal functioning. If one assumes that theta activity indicates that the hippocampus is functioning

in an important and crucial way to determine behavior on these problems, then one would be forced to predict that removal of the hippocampus should result in a deficit on these problems. The simple two-stimulus discrimination used by Adey et al. (1960) is, however, a type of problem learned in normal speed by hippocampectomized animals (Kimble, 1963; Kimble & Pribram, 1963). The two-way active shock-avoidance problem used by Grastyan et al. (1959) is actually learned even faster than normal by hippocampally ablated rats (Isaacson, Douglas, & Moore, 1961). This decisively contradicts the assumption above, and suggests instead that theta rhythms may indicate hippocampal inactivity in behavioral determination, as was first suggested by Grastyan et al.

Early Ideas: Olfaction, Visceral Brain, and Recent Memory

The first serious hypothesis concerning hippocampal function was provided by the early anatomists who argued that the hippocampus must be a higher center for olfaction, as olfactory pathways do enter the hippocampus and other limbic areas after a number of synapses. This idea was supported by the fact that the neocortex lacks an olfactory projection area corresponding to those for vision, audition, and touch. Further, it was most appropriate that olfaction, an ancient sense well-developed in the insectivore ancestors of many of today's mammals, should have its higher center in the limbic system, the ancient brain. For these reasons, the limbic system was termed the nose brain or rhinencephalon, a name which persists in some texts even to the present day. In 1934, Swann showed, however, that learned olfactory discriminations remained intact after the removal of the hippocampus from the rat's brain. Allen (1940) later demonstrated that olfactory discriminations could be learned following removal of the hippocampus in dogs. As was mentioned earlier, there is now reason to believe that the prepyriform, periamygdaloid, and olfactory tubercular areas probably constitute the equivalent of an olfactory projection area, and that the hippocampus receives sensory input from many other sources in addition to the olfactory system. Thus, few investigators would now maintain that the hippocampus or even the greater part of the limbic system is especially concerned with the sense of smell.

The next hypothesis of hippocampal or limbic system function emerged from the research of Kluver and Bucy (1939) and the ideas of Papez (1937) and MacLean (1949). Papez put forward the idea of a functional circuit connecting the hippocampus, mammillary bodies, anterior nucleus of the thalamus, cingulate gyrus, and hippocampus again. This circuit was postulated to be involved in emotional activity. Kluver and Bucy (1939) provided evidence for this hypothesis when they found that a strange behavioral syndrome resulted from very large lesions of the temporal lobe, including much of the amygdala and hippocampus, in monkeys. This behavioral pattern, now termed the "Kluver-Bucy syndrome" included orality and changes in dietary selection, tameness, hypersexuality, psychic blindness, and hypermetamorphosis, which is a tendency to repeatedly examine objects as if they had never been seen before. With this evidence available it was almost inevitable that the limbic system would be postulated to be an emotional or visceral brain with its most magnificent part, the hippocampus, being the control center (MacLean, 1949). The hippocampus was conceived to be necessary for the integration of autonomic and/or emotional functions, and this hypothesis was in high conformity with the evidence then available. When further evidence was gathered, however, it tended to be inconsistent with the idea. Although spatial considerations do not allow a full discussion of this point, the components of the Kluver-Bucy syndrome have since been reported to occur following lesions of the temporal lobe which spare the hippocampus. For example, it is now known with certainty that the tameness observed by Kluver and Bucy was due to amygdaloid damage. Lesions of the amygdala have been found to tame even such normally ferocious animals as the lynx or agouti (Schreiner & Kling, 1956). In addition, none of these emotional symptoms has been reliably reported to occur after lesions restricted primarily to the hippocampus. Hippocampal lesions reportedly

change neither the amount of food consumed (Niki, 1962) nor dietary selection (Gol, Kellaway, Shapiero, & Hurst, 1963). Although no truly definitive study of emotional changes after hippocampectomy has been made, neither the present author nor his associates have been able to detect any consistent or obvious emotional changes after examining hundreds of subjects, including rats, cats, and monkeys. Thus, the idea of the hippocampus as a visceral brain has been generally abandoned in the face of contradictory evidence. Some of this evidence was provided by investigations of human patients following temporal lesions which included the hippocampus—emotional changes were rarely seen, while a striking deficit of an entirely different type was consistently observed.

One of the more dominant ideas of hippocampal function emerged from examination of human patients with large temporal lobe lesions produced in an attempt to alleviate the symptoms of severe mental illness or epilepsy. This lesion was often found to produce striking memory deficits similar to those previously postulated to occur after frontal lobe lesions in monkeys (Jacobsen, 1936). This defect, termed a loss of recent memory, consists of an inability to correctly recall events a few minutes after they have occurred, coupled with an intact ability to recall events which occurred before the operation. The association of the hippocampus with this defect has a long history (see Stepien & Sierpinski, 1964), but decisive evidence for this idea was not available until completion of the investigations of Scoville and Milner (1957) and Penfield and Milner (1958). In the former study, it was shown that the defect does not occur unless the hippocampus is included in the lesion; and in the latter study it was shown that the attention span is normal in patients with recent memory deficits and that they can recall successfully for up to several minutes after exposure to a stimulus. It was also reported that these patients appear to have difficulty in acquiring new skills, which might indicate that the deficit is more than verbal. Learning in man, however, has a large verbal component and this point is not well-established. In any event, the concept of "recent memory" is indistinguishable from "learning ability." Each implies an ability to store new material more or less permanently and to recall correctly upon demand. No permanent learning is possible unless there is a capacity for permanent storage.

The use of the term "recent memory loss" to describe the behavior of patients after hippocampal zone operations has been unfortunately misleading even though the term was well defined by its original users. The reason is that others have used the term "recent memory" and "short-term memory" interchangeably to indicate the short-lived trace effects of a stimulus. By this definition, a recent memory loss would imply that the trace effects of a stimulus would be lost. Such is not the case, however, as Penfield and Milner (1958) specifically demonstrated that the trace effects of a stimulus were intact and that good recall was possible for perhaps several minutes. The defect was that these traces apparently did not become consolidated as permanent memory. The "recent" part of the term refers to recently since the operation, not recently after the stimulus.

Both the recent memory loss idea and studies of hippocampal theta rhythm had the effect of stimulating animal lesion research. Although animal research in this area had its beginnings in the 1930s, its history has not been continuous. Much of the recent research on the behavioral effects of hippocampal lesions stems from work begun in the Isaacson laboratory as recently as 1959. Isaacson and his co-workers were at that time investigating hippocampal theta activity in dogs during the learning of a leg-lift response, and began to wonder how well the animals could learn if the hippocampus were removed. Bilateral hippocampal lesions were made in two dogs, and these were found to learn the response in only a few trials while normal dogs generally required 40 trials or more. These results led to a study of shock-avoidance learning in rats after hippocampectomy, and it was found that these animals learned a double-grill or shuttle-box problem significantly faster than did normal rats or those with neocortical lesions (Isaacson et al., 1961). The apparatus consisted of a narrow rectangular box containing two electrifiable

grids. A buzzer was presented for 5 seconds and the rat was required to cross the opposite grid within this period or be shocked until such a response was made. Identical results were subsequently obtained on two replications, including one blind study, and the results appeared to be well founded. These findings and the earlier ones of Allen (1940) showed beyond a doubt that this lesion did not disrupt a general ability to learn or to store new material. It should be mentioned that the recent memory loss hypothesis is not necessarily disproven by a demonstration of learning if that learning could have occurred within the several minutes allowed for good recall. Isaacson et al. (1961) found, however, that retention was also near-perfect from one day to the next, which demonstrates that permanent storage must have occurred. Kimble and Pribram (1963) later showed that hippocampectomized monkeys actually improve in learning ability as the intertrial interval is extended even up to 6 minutes, far beyond the span allowed by the recent memory loss hypothesis. Thus, the animal data are in contradition to the recent memory loss idea.

A number of studies have now accumulated showing normal learning rates in hippocampally ablated animals on a variety of problems. Kimble (1963) found his hippocampectomized rats to be normal in the acquisition of a simultaneous black-white discrimination. Normal learning of a tactile discrimination problem has been found in cats with hippocampal lesions (Teitelbaum, 1964; Webster & Voneida, 1964). Hippocampally lesioned monkeys have been reported to be entirely normal in the acquisition of a discrimination between numerals (Kimble & Pribram, 1963) or between stimuli differing in size or brightness (Douglas & Pribram, 1966). Normal or superior learning of a straight runway task has been found by Wickelgren and Isaacson (1963) and many others. It has also been reported that hippocampally ablated rats are perhaps even quicker than normals in learning to press a lever for a reward (Clark & Isaacson, 1965; Schmaltz & Isaacson, 1966). Hippocampal lesions obviously do not impair learning in general, even when the learning involves retention for long periods of time. Thus, the animal and human data would appear to be in contradiction. This contradiction could be "resolved" by postulating that the hippocampus has a different basic function in man and beast. Such a solution to this problem is generally unacceptable to physiological psychologists, however. Another possible resolution of this paradox is that the recent memory loss in man is a secondary effect of a different type of primary disorder.

The author has chosen the latter course, and suggests that the recent memory loss in man is a genuine phenomenon, but that it is a byproduct of interference during storage and not due to a lack of ability to store, per se. One of the leading proponents of the single-stage or unitary theory of memory formation (Melton, 1963) maintains that forgetting is primarily a function of interference rather than decay of memory traces, a position held by many others in the area of human memory. An observed deficit in recent memory might conceivably occur even in a subject with intact ability to store and recall if that subject lacked a normal mechanism for the reduction or prevention of interference. Stepien and Sierpinski (1964) provided evidence in favor of this interpretation when they reported that distraction procedures greatly interfered with memory even in those short periods in which normal recall is possible in patients with recent memory deficits. One might argue that if the present position is granted, then these interference effects should also be seen in animals. A counter argument is that such effects may be present but undetectable because of the relatively crude testing procedures used with animal subjects as compared to man. Animal training usually involves a pair of stimuli or responses, one of which is correct and the other incorrect. A human verbal response, in contrast, is often only one out of thousands of possibilities, most of which are "incorrect." The author suggests that the animal equivalent of a recent memory deficit will be found to be excessive generalization, a possibility which has not yet been intensively investigated. That is, hippocampectomized animals should have a flatter generalization gradient.

Recent memory deficits have also been

found to be associated with damage to another part of Papez' circuit, the mammillary bodies. Lesions or tumors in this area often result in recent memory deficits, although in this case the resulting behavior is generally termed "Korsakov syndrome." A case was reported in Barbizet (1963) in which a patient with a full-blown Korsakov syndrome was undergoing shock therapy. This patient invariably insisted that he had never seen the shock apparatus before, yet he always became emotionally disturbed at the sight of the machine. An animal in the same situation might have been found to be normal in shock avoidance and it might have been concluded that no recent memory loss was present. One does not ask an animal questions. It is suggested that the hippocampus might function to protect memory traces during a crucial stage of consolidation through the exclusion of irrelevant and thus interfering stimuli. A theoretical treatment of this possibility is discussed later.

Contradictions in the Animal Lesion Data

The early animal lesion data were plagued by apparent contradictions and inconsistencies which later proved to aid, rather than hinder, the development of ideas about hippocampal function. The finding of superior shock-avoidance learning after hippocampal lesions, though apparently well-established, contradicted earlier reports claiming deficits in shock-avoidance learning after these lesions (Kimura, 1958; Pribram & Weiskrantz, 1957; Thomas & Otis, 1958a). The results of Pribram and Weiskrantz cannot be evaluated because the analysis of the results involved the inclusion of the two animals with hippocampal lesions in a group of animals with a variety of lesions. The reasons for the divergent results obtained in the other two studies became apparent only after McCleary (1961) clarified the issue of avoidance. He found that lesions of the area generally known as the septal region resulted in a grave deficit in the ability to learn to stop approaching a shocked food dish (passive avoidance) but did not interfere with the ability to learn an active shock-avoidance problem of the same type employed by Isaacson et al. (1961). Lesions of the cingulate gyrus had the opposite effect of greatly disturbing active avoidance while not interfering with the acquisition of a passive avoidance response. The latter finding helped to explain the results of Thomas and Otis (1958a), as these investigators had used small dorsal hippocampal lesions which extended upwards into the cingulate gyrus. Furthermore, it was reported that the animals with the most cingulate damage were those which had the greatest deficit. Peretz (1960) and Thomas and Slotnick (1962) later found that rats with lesions of the cingulate gyrus which spare the hippocampus have severe active avoidance learning deficits. Thus, the differences between the results of Isaacson et al. (1961) and Thomas and Otis (1958a) were probably due to the inclusion of the cingulate gyrus in the lesions of the latter study.

The results of the Kimura (1958) study could be explained in a different way. He had found a deficit in passive, not active, avoidance after lesions of the posterior hippocampus, while Isaacson et al. (1961) had found superior learning on an active avoidance task after hippocampectomy. McCleary's dissociation of the two types of avoidance tasks suggested that hippocampal lesions might at the same time enhance active avoidance learning and cause a deficit in passive avoidance. Passive avoidance deficits have since been reported many times to occur after removal of the hippocampus (Isaacson & Wickelgren, 1962; Kimble, 1963; Teitelbaum & Milner, 1963; Kimble, Kirkby, & Stein, 1966; Snyder & Isaacson, 1965). In the Snyder and Isaacson study it was shown that the magnitude of the deficit was a function of the extent of the lesion. This may explain why some investigators who used very small lesions (e.g., Kaada, Rasmussen, & Kveim, 1962; Kveim, Setekliev, & Kaada, 1964) failed to find a passive avoidance deficit while those who used larger lesions did find one. Many of the apparent contradictions in the literature may be traced to the use of small (usually electrolytic) lesions of the dorsal rostral hippocampus in studies which failed to confirm the results of those in which more complete removal was attempted. As was mentioned in an earlier section, even

if these lesions should completely sever the hippocampus (and they often do not), it does not follow logically that the hippocampus is thereby completely inactivated. In addition, small lesions enhance the danger that positive effects might be produced either through irritation or a release of part of the hippocampus from its normal control. Douglas and Isaacson (1964) found, for example, that small electrolytic hippocampal lesions apparently resulted in increased running in the exercise wheel while much larger and more complete lesions did not do so. It is difficult to interpret the first result in terms of loss of function because then this function would also be lost after the larger lesion.

The deficit in passive avoidance found after large hippocampal lesions suggested that the hippocampus might be involved in the cessation of responses rather than in their initiation. Further evidence for this idea was provided by the additional finding of Isaacson et al. (1961) that their hippocampally ablated rats were very resistant to extinction, as extinction also involves the cessation of a response. Increased resistance to extinction after hippocampal lesions has since been found in rats, cats, and monkeys (Douglas & Pribram, 1966; Jarrard, Isaacson, & Wickelgren, 1964; Niki, 1962, 1965; Peretz, 1965; Raphelson, Isaacson, & Douglas, 1966). The idea of an inability to cease responding after hippocampal lesions led to the resolution of yet another contradiction in the literature. Niki (1962) reported that his hippocampectomized rats were, if anything, slightly inferior to normals in the acquisition of an active avoidance response. Procedures used by Niki differed in an important way from those used by the Isaacson group, however, and this difference helped to solidify thinking in this area. Isaacson et al. (1961) had always suspected that their results were less due to fast learning in the hippocampal group than to slow or retarded learning in the normals. They had used a two-way active avoidance task in which the subject was required to return on a given trial to the very compartment in which he had just been shocked on the preceding trial. This appeared to produce a conflict in the normal animals, and they tended to "freeze" much more often than did the hippocampally ablated rats. It was concluded that the two-way active avoidance task must have an inherent and interfering passive avoidance component. An animal with a deficit in passive avoidance, all else being equal, might be expected to learn faster on this problem, as was the case with the hippocampally ablated rats. Niki (1962) had removed this source of interference through using a one-way active avoidance problem. His rats were always shocked in one compartment and never in the other one. Theoretically, this should have removed the advantage enjoyed by the hippocampectomized rats in the two-way situation and differentially enhanced learning in the normal animals, which is precisely what Niki found. Thus, these seemingly contradictory avoidance studies actually complement and explain each other.

It should be mentioned at this time that the profound deficit in two-way active avoidance learning found after cingulate gyrus lesions also largely disappears when a one-way task is used, and that animals with this lesion are even superior to normals in passive avoidance (Lubar, 1964). This evidence suggests that either the cingulate gyrus or the cingulum bundle might normally act to suppress the hippocampus, and that lesions of these areas result in a release of the hippocampus from a normally restraining or controlling influence. This possibility is worth further investigation.

The Deficit Pattern after Hippocampal Lesions

While it was rapidly established that hippocampal lesions do not interfere with learning on some types of problems, it was soon found that these lesions produced considerable deficits on others. In addition to the passive avoidance and extinction deficits mentioned earlier, hippocampal ablations were found to have a deleterious effect on reversal training, even when the prereversal response was readily acquired (Douglas & Pribram, 1966; Kimble & Kimble, 1965; Niki, 1966; Teitelbaum, 1964; Thompson & Langer, 1963; Webster & Voneida, 1964), with the deficit appearing in rats, cats, and monkeys. Even very small hipocampal lesions were found to

disrupt the learning of multiple-cue mazes (Kaada, Rasmussen, & Kveim, 1961; Kveim, Setekliev, & Kaada, 1964; Thomas & Otis, 1958b), and this deficit also appeared after larger suction lesions (Kimble, 1963; Madsen & Kimble, 1965; Niki, 1962). Hippocampal lesions were found to result in an inability to make alternate responses to two stimuli (Gross, Chorover, & Cohen, 1965; Pribram, Wilson, & Connors, 1962; Racine & Kimble, 1965; Rosvold & Szwarcbart, 1964). Normal rats soon begin to stop pressing a lever during presentation of a CS which has been paired several times with shock to the feet (a conditioned emotional response), but rats with hippocampal lesions continue to press normally during this period (Brady, 1958). An enforced delay in the goal box during performance of a straight runway task results in slower running on the next trial in normal rats but not in those with hippocampal ablations (Niki, 1965). After training in a straight runway task, normal rats but not hippocampectomized rats are slowed in their running speed when a tactile distracting stimulus is placed in the runway (Wickelgren & Isaacson, 1963). In a similar study, Raphelson, Isaacson, and Douglas (1965) failed to find significant differences using the tactile stimulus, but found their group with large hippocampal lesions to be less than normally distracted by a visual stimulus. Douglas (in press) found his hippocampally ablated monkeys to be much less than normally distracted from an ongoing sequential response by the presence of a loud auditory stimulus, but to be as distractable as normals when stimuli resembling the task cues were used or when offset of house lights was used as a distractor. Thus, subjects with hippocampal lesions are apparently either equal to normals in distractability or less than normally distracted, depending upon the conditions of the test. It must be remembered, however, that these results were found only in cases where distractability was measured against a very powerful ongoing response.

Clark and Isaacson (1965) found that hippocampectomized rats could not learn to wait 20 seconds between bar-press responses if they had first been trained on a continuous schedule. They can learn if not so pretrained, however (Schmaltz & Isaacson, 1966). Ellen and Powell (1962) did not find significant group differences on a task somewhat similar to that of Clark and Isaacson (1965), but the lesions were very small in comparison to those of the latter study. In a later report, Ellen and Wilson (1963) found an inability in their hippocampally lesioned rats to switch from a response of continually holding the lever down to one in which it was pressed and released, and vice versa. Niki (1965) found that hippocampectomized rats do not have the normal depression in bar pressing rates when a signal is introduced which indicates that no reinforcement will ensue during its presence. This finding was confirmed by Swanson and Isaacson (1967). Jarrard (1965) also found that switching from a continuous to a variable interval bar-press schedule resulted in reduced pressing rates in the normal rats as compared to those with hippocampal lesions. Kamback (1967) found that if two levers are present and one of them rewarded with presentation of a light and the other not rewarded, both hippocampally ablated and normal rats initially preferentially press the reinforced lever, but the normal rats eventually lose this preference while hippocampally ablated subjects do not.

Kimble and Pribram (1963) found that hippocampectomized monkeys have great difficulty in learning to press two stimuli in sequence when they are simultaneously presented. Finally, it has been reported that hippocampally ablated rats have a deficit in learning to make a successive discrimination in the T or Y maze (Kimble, 1963) even though they have no difficulty in learning to respond differentially to the same stimuli when they are presented simultaneously instead of successively.

Nature of the Deficit

Two of the first ideas to emerge from a consideration of the animal data were that hippocampectomy might result in a state of high drive or that it might produce an inability to withhold a response (perseveration). These ideas occurred simultaneously to many investigators and can justly be attributed to no single person. The high-drive hypothesis would explain the data in terms of complex-

ity. The high drive level assumed to be present in the hippocampectomized animals should result in superior performance on the very simplest tasks, with a progressively larger deficit on the more difficult tasks as a function of increasing complexity. Few ideas have been more contradicted by the data. This hypothesis demands, for example, that hippocampectomized animals be more superior to normals on the one-way active avoidance task than on the two-way, which is demonstrably more difficult or complex by any definition. Quite the reverse has been shown to be true. Kimble (1963) also found that his hippocampally ablated rats were comparatively less deficient in the maze configuration which was the more difficult for the normals to learn. This hypothesis would also predict that hippocampectomized rats would run more in the exercise wheel than normals, as there is some evidence that this is one of the responses most sensitive to deprivation changes (Strong, 1957). Douglas and Isaacson (1964), however, confirmed the earlier findings of Rasmussen, Kaada, and Bruland (1960) and Kaada, Rasmussen, and Kveim (1961) that hippocampal lesions do not change running activity in the wheel, either in total amount or in temporal pattern. Kim (1960) also failed to find a significant change in tambour cage activity after hippocampal lesions in rats. As is shown later, reports of increased activity after hippocampal lesions usually refer to a lack of habituation or time decrement rather than to a multiplication of normal activity. The high-drive hypothesis has been generally abandoned.

The second idea provides a much better fit for the data. In the studies discussed so far, it has repeatedly been found that the hippocampectomized animals excel over the normals on tasks in which a disruptive inhibitory tendency is present, are normal on tasks in which no inhibition is involved, and are inferior to normals on tasks demanding an inhibitory tendency. Most of the items on the preceding lists fit into this overall pattern without further explanation. Others, however, do not so obviously fit into this pattern and thus an analysis is required of the responses involved in those cases. Examples are the deficits in maze learning, sequential learning, and successive discrimination, none of which can be said to crucially involve inhibition without further explanation.

Kimble and Pribram (1963) found their hippocampectomized monkeys to have a very large deficit in learning to respond to two stimuli in sequence when both were simultaneously present, whether the sequence was externally or self-ordered. The mistakes made by these animals were far from being random, however. All of the subjects, whether normal or lesioned, initially developed a powerful tendency to press the stimulus which immediately preceded the reward on those trials where a reward was delivered. The normal animals, however, were able to eventually overcome this apparently "natural" tendency and switch over to pressing the stimulus which did not immediately precede the reward before pressing the one which did. The failure of the hippocampally ablated subjects on this task could then be attributed to a failure to withhold the prepotent response. The results of Kimble and Pribram (1963) have been interpreted as indicating that removal of the hippocampus results in an inability to learn a sequence per se. Evidence against this interpretation and in favor of the present one was provided by Douglas (in press). In that study, a sequence was used which did not require the cessation or inhibition of a response, and hippocampally ablated monkeys were found to learn even faster than normals. Stimuli were presented one at a time, and the animal was required to press a first stimulus in order for a second one to appear. A press of the second stimulus was then rewarded with a peanut. This problem is sequential in that a first response must be made with no direct reward in order to have the opportunity to make a directly rewarded response. Thus, there is presently no proof for a contention that hippocampectomy disrupts an ability to learn a sequence of responses per se.

Once again, it is not obvious to all that maze learning requires an inhibitory process. Kimble (1963) noted, however, that the poor performance of his hippocampally ablated rats in the maze was accompanied by repeated reentry into blind alleys, which inflated the error score. Kveim, Setekliev, and

Kaada (1964) reported that their hippocampally lesioned rats made many more errors than the normals even on the first trial, before any response could legitimately be considered an error. Niki (1966) found his hippocampectomized rats to lack flexibility in their choices of pathways in a Dashiell maze, and Leaton (1965) found hippocampally lesioned rats to be more than normally perseverative in their maze decisions. In addition, Roberts, Dember, and Brodwick (1962) and Douglas and Isaacson (1964) found hippocampectomized rats to entirely lack the normal tendency of the rat to avoid entering the same side alley of a T maze on two consecutive trials (spontaneous alternation). Thus, the difficulty in maze learning observed in the hippocampally lesioned rat can be explained as being due to the lack of a normal ability or tendency to avoid alley reentry when the response is unreinforced. This explanation agrees with the ideas of Dennis and Sollenberger (1934) that complex maze learning involves "negative adaptation" to the blind alleys, with this effect being removed through reinforcement in the correct alleys.

The deficit in successive discrimination after hippocampectomy (Kimble, 1963) is a more difficult one to explain. The basic design of this problem is that the subject is required to make one response when both side alleys of a T or Y maze contain inserts of one type (e.g., black) and to make the opposite response when both alleys contain inserts of another type (e.g., white). This would appear to be a combination of two very simple problems, each of which could be learned independently. This is, however, one of the more difficult problems for a normal rat to solve. Isaacson, Schmaltz, and Douglas (1966) have recently completed an intensive investigation of this problem. They found that normal rats invariably develop a strong turning habit (the term is purely descriptive) which is then abandoned just prior to an improvement over chance success on this problem. Rats with hippocampal lesions, however, continue in their maladaptive turning habits and do not learn. While there is no proof that perseveration is the cause, rather than the effect, of the inability of hippocampally ablated rats to learn this problem, these findings are in agreement with the present line of thought.

The perseveration or lack of inhibition hypothesis can also help to explain a contradictory finding which has not yet been discussed. Niki (1962), in contrast to many other studies, found deficits after hippocampal removal on two different simple discrimination tasks. The first involved the requirement that the subject make an approach response to an alley in which an electric light was lit. It is known, however, that rats tend to enter the darker of two alleys, even when the brightness difference is much less than that used in Niki's (1962) study (Douglas & Isaacson, 1965). Thus, the failure of the hippocampally lesioned rats to learn in normal speed may have been due to an inability to readily overcome this tendency. Niki (1962) also used a more difficult discrimination problem, involving vertical versus horizontal stripes, and the deficit in the hippocampally ablated group was relatively less on this problem than on the first one. The deficit did occur, however, and the findings are thus not in agreement with several others mentioned earlier. The training procedure used by Niki differed considerably from those used by other investigators in that a plastic door was placed in front of the alleys and the subject was not allowed to actually enter the incorrect alley. An error was scored when this door was touched. While it is difficult to evaluate what effect this procedure might have had on the normal or lesioned animals, it might conceivably have differentially enhanced the scores of the normal subjects. If this possibility is true, then one could add a constant to both problems and deduce that the hippocampally ablated animals were relatively worse on the problem in which they were required to approach the light. Otherwise, one must grant that contradictions will occasionally occur, as one might expect from a consideration of statistical methods.

On many of the tasks mentioned earlier, the presence or absence of inhibition seems intuitively clear, but there is also some independent evidence for the presence of an inhibitory variable in some cases. Pavlov

(1927), for example, presented considerable evidence that extinction must involve an active inhibitory process. Brimer and Kamin (1963) deduced that the conditioned emotional response which does not develop in hippocampectomized rats (Brady, 1958) must be an inhibitory phenomenon because it is susceptible to disinhibition by preshock.

There were two schools of thought among those who inclined towards the response-inhibition hypothesis. The first insisted that the hippocampus is involved in the inhibition of only learned responses, while the second included both learned and unlearned responses, provided that they occur with high probability. To the latter group, learning was only a special case of making a reponse more probable and thus amenable to study. Kimble, Kirkby, and Stein (1966) provided evidence in favor of the learned-response hypothesis when they found that their hippocampally lesioned rats had the usual passive avoidance deficit when a learned response was used, but that they had no such deficit when an unlearned "step-through" response was used. This report is in contradiction to the findings of Teitelbaum and Milner (1963) that hippocampally lesioned rats were unable to learn to not stray off of an unshocked platform onto a shocked grid. Isaacson, Olton, Bauer, and Swart (1966) have argued that the negative results of Kimble et al. (1966) were due to the use of a weak or improbable response. When Isaacson, Olton, Bauer, and Swart (1966) employed the presumably more powerful unlearned tendency of the rat to step off a shaking platform they did find a passive avoidance deficit in their hippocampectomized rats. The unlearned response idea has support from many other studies. For example, the high tendency of the rat to avoid entering the same side alley of a T maze twice in a row is apparently unlearned (Smith, 1962), but this tendency is totally abolished after hippocampal removal, as was discussed earlier. In addition, normal rats begin exploring a strange environment with a high rate of activity (provided they are gentled animals) but become markedly less active with time of exposure. Hippocampally lesioned rats begin exploring at the same rate as normals but fail to have the usual marked decrement with exposure (Douglas & Isaacson, 1964; Roberts et al., 1962; Teitelbaum & Milner, 1963). Douglas (in press) found hippocampectomized monkeys to be lacking in habituation to a distracting stimulus. In these cases, the response to be inhibited was not a learned one in the usual sense of the term. Thus, the inhibitory function of the hippocampus is far from being restricted to learned responses, but covers a wide range of unlearned behavior as well.

Specificity of Lesion Effects to the Hippocampus

So far the symptoms following hippocampal lesions have been discussed as if they were not also found after lesions of other brain areas, but this remains to be demonstrated. It is inevitable that lesions of even functionally independent brain structures will result in similar changes in behavior on some tasks because there are many reasons why a subject might do poorly on any one problem. It is highly unlikely, however, that lesions of truly independent brain areas will consistently produce the same overall patterns of deficits on a variety of different problems. Thus, the pattern of effects observed after hippocampal lesions will be compared to the patterns found after other lesions. With the exception of motor and sensory projection areas, which are not considered here, most brain areas have not been as intensively investigated as the hippocampus. The present discussion includes those areas about which enough is known for at least rudimentary comparisons.

There can be little doubt that lesions of the lateral posterior neocortex in rats do not produce symptoms such as are observed after hippocampectomy. In many of the studies cited earlier, rats with these cortical lesions were included as a control group and their behavior was usually significantly different from that of the hippocampectomized group and indistinguishable from that of a normal control group.

Cingulate gyrus damage produces effects opposite to those of hippocampal ablation on both passive avoidance and two-way active avoidance. This information is more than suf-

ficient for a demonstration that the two areas must function differently.

Ablation of the amygdala also produces many effects which are opposed to those of hippocampal lesions. Amygdalectomized cats have a large deficit in learning a two-way active avoidance task (Brady, Schreiner, Geller, & Kling, 1954; Horvath, 1963), and monkeys with amygdaloid lesions are normal in habituation to a distracting stimulus (Douglas, in press). It was found by Douglas and Pribram (1966) that monkeys with hippocampal and amygdaloid lesions differed as much from each other on a series of tests as either differed from animals with intact brains.

Hippocampal and caudate nucleus lesions produce distinctly different effects. It is well known that unilateral caudate lesions produce turning and that bilateral lesions result in obstinate progression. Bilateral caudate lesions do not produce the deficit in maze learning which is associated with hippocampal lesions (Chorover & Gross, 1963), but they have been reported to result in passive avoidance deficits (Fox, Kimble, & Lickey, 1964). The latter result may, however, be due to obstinate progression and may not be related to a similar-appearing deficit after hippocampectomy.

It is difficult to decide whether hippocampal and frontal lesions produce similar results or not because investigators of the two areas have tended to use widely different problems and procedures. Both the frontal lobes and the hippocampus have been implicated in recent memory, although for entirely different reasons. The recent memory deficit after hippocampal lesions was based on observations of human patients and is not an adequate description of animal behavior after the lesion. The memory defect after frontal lesions was deduced from animal behavior, mainly the inability to learn a delayed response, and is not ordinarily observed in human patients with prefrontal lobotomy. There can be little doubt that frontal lesions produce a large deficit in delayed-response learning, for whatever reason, but this effect is not consistently found after hippocampal lesions unless delayed alternation is tested (Rosvold & Szwarcbart, 1964). The two lesions also produce different GSR effects. While hippocampally ablated monkeys have normal galvanic responses to a strange tone (Bagshaw, Kimble, & Pribram, 1965), monkeys with frontal lesions have flat records much like those seen after amygdalectomy (Grueninger, Kimbel, Grueninger, & Levine, 1965). The possibility cannot be lightly dismissed that the frontal lobes exert some control over limbic functions, as this region has connections with the amygdala and hippocampus, in the latter case via the cingulum bundle. Both this possibility and a more direct comparison between the effects of frontal and hippocampal lesions await further investigation, but preliminary results of studies presently underway in Pribram's laboratory strongly indicate a divergence in behavior on several tasks after the two lesions.

Lesions of the hippocampus and the septal region do produce similar effects on a number of problems. Septal lesions result in faster than normal learning in the two-way active avoidance task (King, 1958) and in very poor passive avoidance learning (Kaada, Rasmussen, & Kveim, 1962) in the rat. Septal lesions also abolish spontaneous alternation (Douglas & Raphelson, 1966b) and impair acquisition of a conditioned emotional response (Brady & Nauta, 1953). The effects of the two lesions on other types of behavior are markedly different, however. Septal lesions produce a transient extreme hyperirritability or rage (Brady & Nauta, 1953) in some animals, although the other behavior changes are not dependent on this effect. Septal lesions produce only a slight impairment in complex maze learning, and many of the errors which are made appear to be due to overexcitement (Thomas, Moore, Harvey, & Hunt, 1959). Douglas and Raphelson (1966a) found their septally lesioned rats to be less active than normal in the exercise wheel, initially more active than normal in exploration of a strange cage, but normal or superior in subsequent habituation of exploratory responses. In contrast, hippocampectomized rats are normal on all of these responses but habituation, where they have a large deficit (Douglas & Isaacson, 1964). Since septal lesions invariably involve massive fornix damage, these divergent results sug-

gest that the hippocampus can at least partially function after fornix section.

The Narrowing of Hypotheses

In summary of the discussion so far, the changes in behavior found after removal of the hippocampus are almost invariably of a perseverative nature when a prepotent response is involved, implying that the basic function of the hippocampus is inhibitory, although the nature of this hypothetical inhibition has not yet been discussed. The full range of behavioral changes observed after hippocampal lesions is not found after lesions of any other part of the brain. The data have been shown to be inconsistent with a number of hypotheses including the emotional and visceral and olfactory brain concepts, the recent memory loss idea, the idea that the lesion produces a selective deficit in the learning of sequential behavior, the high-drive hypothesis, and the idea that the hippocampus inhibits only learned responses. Ideas not yet examined are that the hippocampus is a site for long-term memory storage, that it is necessary for response discrimination, and that it is necessary in a different type of recent memory function than has been discussed so far.

The first of these ideas is obviously contradicted by the fact that human patients with hippocampal zone operations have good recall for memories stored before the operation, indicating that stores have not been lost. Animal studies bearing on this subject are those in which a response is learned preoperatively and tested or relearned postoperatively. These studies have had mixed results. In some cases a retention deficit has been reported (e.g., Niki, 1962) while in others no deficit has been found on tasks which originally probably required an intact hippocampus for efficient learning (Douglas & Pribram, 1966). In studies such as these, negative results should probably be given little weight because a retention deficit can be due to a variety of variables such as the degree of overtraining, temporary retrograde amnesia, loss of ability, etc. If the hippocampus actually were a site for long-term memory storage, these deficits would be large and consistently found, while in fact they are neither.

Many studies have demonstrated that hippocampal ablations do not affect discrimination learning when no inhibition is involved, even when complex pattern stimuli are used. Thus, the hippocampus is not necessary for discrimination per se, or for making decisions between two stimuli or responses when none of these is prepotent. These findings argue against the ideas expressed in Adey, Dunlop, and Hendrix (1960), based on studies of theta rhythm, that the hippocampus is specifically involved in judgmental or discriminative functions. Thus, the idea is dropped from consideration here.

Lash (1964) postulated that the hippocampus must be involved in response discriminability. Unfortunately, the analysis of the one study which did appear to support this idea involved the use of assumptions which, though reasonable at the time, have since been disproven. One of Lash's key assumptions was that his animals were spontaneously alternating body turns, while Douglas (1966) has since demonstrated that alternation of body turns does not occur. It is, however, possible to explain some of the results in the literature in terms of a lack of response discrimination. A passive avoidance deficit might be explained as being due to an inability to discriminate the positive from the negative response, and normal learning after hippocampectomy on some problems might be explained as resulting from the noninvolvement of response cues. There are many more results which do not conform to this way of thinking, however. The maze learning deficit found after hippocampectomy cannot be ascribed to a lack of an ability to discriminate turning responses because it has long been known that rats do not simply learn to make a series of turning responses in the maze, although their behavior is often described in this way as a matter of convenience. Hunter (1920) demonstrated that rats have extreme difficulty in learning to make even the simplest types of turning sequences when spatial and other cues are eliminated through the use of a "temporal maze." Another example of behavior which cannot be analyzed in terms of response discrimination

was reported in Douglas and Pribram (1966). In that study, it was found that hippocampectomized monkeys had no difficulty in learning a conventional discrimination task where one stimulus is always rewarded and the other one never reinforced, but they had a large deficit in learning to maximize when one stimulus was rewarded 70% of the times it was responded to and the other 30%. Response discrimination was no more involved in one case than in the other. The inhibition idea, on the other hand, has no difficulty with this finding. North and McDonald (1959) have pointed out that this differential partial reinforcement task should be very difficult to learn in a purely excitatory fashion. Learning (maximizing) curves both for their subjects and for the normal animals of Douglas and Pribram (1966) show a sudden improvement in success which cannot be accounted for in terms of reinforcement alone. The latter authors suggested that this jump in the success curve signified the initiation of an inhibitory process acting on the least reinforced of the two stimuli or responses. This suggestion is supported by the finding that the curve for the hippocampally ablated group rose very gradually to the 90% level, with no sign of such a jump in success. Furthermore, the normal animals were later shown to have apparently developed an "aversion" for the least reinforced stimulus because they preferentially responded to a novel stimulus when it was paired with the former least reinforced cue. The hippocampally ablated monkeys did just the opposite on this test, which suggests that they had developed only positive tendencies toward both partially reinforced stimuli used in the preceding test. Thus, the response discriminability hypothesis is dismissed from consideration here not because it has been disproven, but because it lacks analytical or predictive power in a great many situations in which the behavior of hippocampectomized animals diverges considerably from normal.

While one version of the recent memory loss hypothesis was earlier shown to be inconsistent with the animal data, even though the idea is valid on a descriptive level. There is another version which differs considerably from the first. Konorski, Stepien, and others conceive of a brain mechanism in which the trace of a stimulus is "held" or retained in an active form for a period of time in which it can be compared to subsequent stimuli. A defect in this hypothetical mechanism is not the same as a defect in recent memory according to the earlier definition, because in that case the traces were assumed to be normal, as was shown by the presence of a normal attention span (Penfield & Milner, 1958). The association between this second recent memory function and the hippocampus rests largely on the results of two experiments. In the first, monkeys with lesions including much of the hippocampus were found to be unable to learn a task requiring them to make a positive response when each of two temporally separated stimuli were equal and to withhold the response when they were different (Stepien, Cordeau, & Rasmussen, 1960). The results showed, however, that this failure was almost entirely due to errors of commission or perseveration, as the response inhibition hypothesis would predict, and the results thus support the latter idea more than the one intended. In a second study, human epileptic patients were used as subjects with the assumption that the hippocampus could not function properly because of abnormal electrical activity (Stepien & Sierpinski, 1964). These subjects were also highly deficient on a task similar to that used with the monkeys. In this case retention was unimpaired at intervals of up to about 1 minute between stimuli but greatly impaired either at the longer time intervals or when distraction procedures were used at the shorter intervals. This evidence is actually more supportive of the earlier version of a recent memory loss than this later one, and also tends to support the idea that the deficit is due to interference effects. It seems clear that a valid demonstration of this type of memory deficit, with other plausible possibilities eliminated, should involve a task which does not require inhibition or demand long-term memory storage. Correll and Scoville (1965) performed an experiment theoretically measuring this holding ability but using two positive responses as indicators. They used a delayed matching from sample paradigm in which a single color

stimulus was presented to a monkey which was rewarded for touching it. The stimulus was then withdrawn and, after a time interval, a pair of color stimuli was presented to the subject. The subject was then rewarded for touching the stimulus which was identical to the first. This task did not simply involve a response to a particular stimulus because the color of the positive stimulus was varied from one trial to the next and on each discrimination trial the subject was required to remember the color of the preceding single stimulus. The results were that the subjects with lesions confined to the hippocampus and hippocampal gyrus were entirely normal on this problem. Drachman and Ommaya (1964) found only a slight deficit on a similar task in monkeys with combined lesions of both the amygdala and hippocampus. In a later study using human subjects with inferred hippocampal lesions, Drachman and Arbit (1966) found retention to be relatively unimpaired when lists were used with items falling within the attention span range but greatly impaired when this number was exceeded. These results, and many others, tend to support the earlier version of a recent memory loss idea more than the later one, and do not rule out the possibility of interference as a causal factor.

While one might be tempted to dismiss the later variant of the recent memory loss idea, it is still possible that the basic idea could prove useful after a slight revision. For example, it could be modified into a "working memory" hypothesis. The working memory is a hypothetical function in which various central representations of stimuli, including some called up from permanent store, could be intergrated and the new combination then stored in permanent memory. There is no reason why permanent storage could not still take place even in the total absence of this working memory, but the stored material would tend to be disorganized and lack integration or sorting for relevance unless these were externally imposed by the situation. One could then explain the inability of hippocampally lesioned animals to withhold a response as being caused by an inability to recategorize the response-inducing stimuli. The human recent memory deficit would then be theoretically the result of interference during storage due to the lack of a mechanism for the sorting, categorizing, and organizing of stimuli for storage and an inability to exclude the irrelevant. While this idea appears to have some promise, it has not yet been worked out in enough detail for definite predictions to be made in many situations. For this reason, its value in the analysis of the effects of hippocampal lesions is more potential than actual at the present time. The author believes, however, that this idea might eventually prove to be a formidable competitor with the inhibition concept.

Refinement of the Inhibition Concept

The response inhibition idea of hippocampal function appears on the surface to be simple, straightforward, and successful in the analysis of the lesion data. It suffers, however, on closer analysis. It has been amply documented that animals simply do not learn to make "responses" or muscle movements in many or even most of the problems commonly used by investigators of animal behavior. Lashley and Ball (1929), for example, showed that if rats are first trained to correctly run through a complex maze and then subjected to spinal cord lesions which make normal locomotory responses impossible, they will subsequently stagger through the maze with scarcely an error. Similar results have been found before and since that study, and it is now clear that the term "response," as generally used in psychology, refers to a class of acts which may and do differ widely in the precise muscle movements involved in each, but which are united by the fact that they have similar effects or outcomes. Responses, in other words, are results. Thus, if animals do not learn to make muscle movements in the first place it is unlikely that the cessation of an act involves inhibition of muscle fibers.

Even aside from this argument, however, animals with hippocampal lesions are often said to be perseverating in a response even though the response does not continue in the absence of the appropriate stimulus. Hippocampally ablated animals do not continue to walk until they bump into a wall (as do animals with caudate lesions), continue to eat until stuffed (as do animals with ventro-

medial hypothalamic lesions), or continue to groom or scratch for prolonged periods of time once these responses have been initiated. Thus, they are fully able to cease making a response when the initiating stimulus is no longer present. For this reason, even a more molar use of the term response still does not lead to an adequate description of the behavior of hippocampally lesioned animals until the term is expanded to the point where it includes something other than muscle movements. The response inhibition idea must therefore be modified into a more sophisticated form which retains the value of the original naïve concept while eliminating its weaknesses. The present author can conceive of two such possibilities. The first is that the hippocampus inhibits neither muscle movements nor patterns or sets of muscle movements, but bonds, connections, or associations between stimuli and responses. While the author knows of no investigator overtly holding this hypothesis, it is covertly held by many who view the response in terms of outcomes or results because in these cases inhibition could occur before movements of any type were even initiated. The second possibility is that the hippocampus inhibits attention to a stimulus and/or reception of the stimulus which normally initiates the response. Gebrandt (1964) suggested that a great deal of behavioral and physiological data, including active and passive avoidance results, could be interrelated if it were assumed that passive avoidance is a subset of the class "inhibit-attentive-responses" and that this class had a neutral substrate similar to the Papez circuit discussed earlier. This basic position has been independently adopted by Douglas and Pribram (1966) in their model of limbic function, although the basic function has been restricted to the hippocampus. This model is discussed in detail later.

Both of these modifications of the response inhibition concept are fully capable of handling the data presented earlier, and both give the subject the added option of ceasing to respond when response-inducing stimuli are absent. It is of interest that while these ideas give the appearance of differing fundamentally, they make similar predictions. Both are also functionally similar to Pavlov's (1927) concept of internal inhibition and could, in fact, be claimed to *be* internal inhibition. For example, both extinction and the inhibition of an orienting reflex (habituation) were postulated by Pavlov to involve internal inhibition. By analogy, a similar claim could be made for reversal training and passive avoidance, although Pavlov did not devote his thinking to these phenomena. Thus, it could be claimed that the hippocampus is the site or organ of internal inhibition, and because of the theoretical elaboration which has been made of this concept, a loss of internal inhibition must be considered to be a prime possibility for explaining the effects of hippocampal lesions on behavior. This does not, however, eliminate the other two ideas from consideration because Pavlov's (1927) data could be claimed to support the other two ideas as well as his own. Furthermore, one drawback of the Pavlovian model has been its failure to develop a plausible neural mechanism to complement its excellence on the behavioral description level. The other ideas suggest possible brain or neural mechanisms which may prove to be more "correct."

While the idea that the hippocampus might function to inhibit stimulus-response bonds has yet to be theoretically elaborated, the idea of attention control through inhibitory modulation of sensory input is a major part of the Douglas-Pribram (1966) model. In that model, the hippocampus is postulated to exclude stimulus patterns from attention through a process of efferent control of sensory reception known as gating. There are two hypothetical types of gating mechanisms, one of which is known as nonspecific gating because it results in the widespread exclusion of irrelevant stimuli during the process of the concentration of attention. This type of gating corresponds to Pavlov's (1927) external inhibition. Nonspecific gating has been postulated to have the function of protecting memory traces from interference during consolidation, and the recent memory loss is theoretically caused by the lack of nonspecific gating and the consequent presence of interference with selective consolidation.

The other type of gating is known as specific gating because it acts to inhibit re-

ception of specific stimuli which have been associated with nonreinforcement. The specific gating system is postulated to be involved in habituation (the purest example), extinction, reversal, active error reduction, passive avoidance, and in other allied types of decremental behavior. In a later version of this model, which is presently being prepared for publication, the specific gating system also functions in perceptual sets, the sharpening of discriminations, and in repression. Both repression and passive avoidance are now viewed as special cases of the action of specific gating mechanisms in the "solution" of approach-avoidance conflicts through diverting attention away from conflict stimuli. The specific gating system is congruent with Pavlovian internal inhibition on the behavioral description level.

The Douglas-Pribram model also includes an amygdaloid function which is termed the "reinforce-register system." This system is postulated to increase the probability of attention to a stimulus as a function of its association with reinforcement, whether positive or negative. This function is carried out through the enhancement or facilitation of the appropriate sensory input. This system is important in the consideration of the behavior of animals with hippocampal lesions because it is presumably intact in these animals and helps to explain the behavior of which these animals *are* capable. The function of this system is almost identical to Pavlov's (1927) excitation.

Both the amygdaloid and hippocampal attention-directing systems are believed to be involved in the Gestalt variables of figure and ground. The amygdaloid system makes stimuli more figural, while the hippocampal system converts figure into ground. The latter could be taken to be a definition of habituation at this level of discourse. Support for this content has been provided by Weitzman (1963). He found a lower threshold for line detection when the stimulus was located within a figure and a higher threshold when it was located within ground. He suggested that his results could have been due to a modification of stimulus input.

The isomorphism between the Douglas-Pribram and Pavlovian models was not the result of deliberate planning, as the former was developed purely as a consideration of how behavior might be controlled by attention-directing mechanisms. As the model became more inclusive, it began to resemble that of Pavlov (1927) to a remarkable extent, and the Douglas-Pribram model could legitimately be said to be a restatement of Pavlov in attentional terms. The neural mechanisms recently devised as a substrate for the Douglas-Pribram model in fact suggest plausible neural events which might underlie some of Pavlov's most well-established yet mysterious data on the interplay between inhibition and extinction.

In the revised version of the Douglas-Pribram model, a much simpler, though not necessarily more valid, neural mechanism has been postulated to be involved in the efferent control of sensory perception than was first suggested in Douglas and Pribram (1966). In the latest version, this control is carried out through inhibitory and facilitatory control of recurrent inhibitory feedback loops in the sensory systems. The basic element in this network is a loop from a sensory relay cell which contacts a Renshaw-like interneuron. This interneuron, in turn, makes an inhibitory synapse with the original sensory cell. Each sensory cell has many such loops, and these contact the Renshaw-type cells associated with neighboring sensory cells, with the probability of such contact being an inverse function of distance. This network is basically equivalent to that postulated by Ratliff, Hartline, and Miller (1963) to exist in the visual system of the horseshoe crab, with the major difference being that those authors made no use of interneurons. Data indicating that such inhibitory loops must exist and that they are controlled by the higher centers of the brain through fibers which contact the interneurons can be found in Gordon and Seed (1961), Towe and Jabbur (1961), Jabbur and Towe (1961), Eccles (1964), Andersen, Eccles, Schmidt, and Yokota (1964), Andersen, Eccles, Oshima and Schmidt (1964) and Walberg (1965), to mention but a few of the many articles bearing directly on this point. In these studies the evidence suggests that inhibitory loops functionally equivalent to the one presently

postulated must exist in the sensory relay nuclei and that facilitation and inhibition of activity in sensory channels involves efferent control pathways which synapse with the interneurons and not directly with the sensory units. For this reason, the inhibitory control of sensory reception by the hippocampus is postulated to be mediated by fibers which make excitatory synapses with the Renshaw-like interneurons, which then inhibit activity in the associated sensory channels. The facilitatory action of the amygdala is postulated to involve an inhibitory synapse with the Renshaw-like cell, with the overall result then being a sensitization of the affected channels for sustained input. The major problem with this analysis is that control of sensory input has so far been mainly associated with neocortical areas. Many of the studies in the list above demonstrate inhibitory and facilitatory control over somatosensory input following stimulation of sensorimotor cortex. Dewson, Nobel, and Pribram (1966) presented evidence indicating the removal of a tonic inhibitory effect in the auditory system after removal of insular-temporal (auditory association) cortex in the cat. Stimulation of inferotemporal cortex in the monkey was found to have an inhibitory effect on visual input in that it resulted in a lengthening of the visual recovery cycle (Spinelli & Pribram, 1966). It should be noted, however, that in each of these cases a cortical area was found to exert control over a specific sensory system. In each case, the given area was apparently the only one in which stimulation influenced reception in the given system, and in no case did stimulation of the given area affect evoked potentials or recovery cycles in any other system. Logically, however, even the simplest efferent sensory control system must involve simultaneous control of several senses. The author suspects (and the model demands) that these master control areas will be found to be the amygdala (facilitation) and the hippocampus (inhibition). Amygdaloid stimulation has already been found to have a facilitatory influence in the visual input system (Bagshaw, 1965), but for technical reasons her auditory records could not be properly analyzed. Feldman found that hippocampal stimulation inhibited evoked potentials produced in the posterior lateral hypothalamus by sensory or lemniscal stimulation. Fox and O'Brien (1962) mentioned that preliminary investigations indicated that hippocampal stimulation had a primarily inhibitory effect on visual evoked potentials. If further research should bear out these early findings, then the Douglas-Pribram model would be vindicated on both the behavioral and neurological levels. This would constitute a large step forward in the integration of behavioral-lesion, electrophysiological, and drug studies, since the "hardware" required for the Douglas-Pribram model also theoretically produces EEG waves when unmodulated (see Eccles, 1964) and helps to explain many otherwise divergent phenomena. For example, facilitatory effects in this system produce an inhibitory surround while inhibition produces an excitatory surround for the same reason that the functionally equivalent network of Ratliff, Hartline, and Miller (1963) detects edges. This provides a neural underpinning for the observations of Pavlov (1927) that inhibition and excitation induce one another.

In addition, the hypothetical employment of a Renshaw-like interneuron in the network suggests that gating fibers must secrete acetylcholine at their excitatory synapse with the interneuron, because Renshaw cells are known to be excited by a synapse from the cholinergic motor horn cell via a recurrent loop. This suggests that hippocampal function could be blocked at the periphery through the use of a selective anticholinergic compound whether or not this drug directly affected the hippocampus. Significantly, the anticholinergic drugs of the belladonna family have been found to duplicate the effects of hippocampectomy on such a wide range of problems that the similarity cannot be coincidental (Carlton, 1963; Douglas & Isaacson, 1966). These drugs, in proportion to their central effectiveness, also have the effect of blocking hippocampal theta activity through disrupting rhythmic firing in septal pacemaker cells (Stumpf, 1965), and the present author formerly thought that this might be the reason why such drugs as scopolamine were behaviorally equivalent to hippocampectomy. This cannot be the entire

reason, however, because septal lesions also block theta activity (Green & Arduini, 1954), but they do not interfere with a prime example of behavior requiring the hippocampus, habituation (Douglas & Raphelson, 1966a). The latter finding suggests that the hippocampus can still function at least in part after fornix damage, as it is extremely difficult to make a septal lesion without massively damaging the fornix. The present analysis also suggests a more consistent reason why the belladonna drugs produce hippocampectomized effects. This analysis presupposes, however, that the hippocampus and amygdala will be found to control sensory input in the manner prescribed by the Douglas-Pribram model in its more recent revision.

In summary, the present analysis has attempted to demonstrate that hippocampal lesions produce a unitary deficit consisting on the descriptive level of an inability to withhold a response. The data have been shown to be inconsistent with a number of ideas including the olfactory, visceral, and emotional brain concepts, two versions of a recent memory loss idea and a memory storage site concept, the hypothesis that the hippocampus is primarily involved in response discrimination or that it is necessary for discrimination or judgment in general, the high-drive hypothesis, the idea that the hippocampus is primarily involved in sequential learning, the hypothetical restriction of hippocampal function to learned responses, and the idea that the hippocampus acts to directly inhibit muscle movements. While the latter possibility was not entirely excluded, it was shown that it could not by itself explain the effects of hippocampectomy.

Four ideas have apparently survived the present analysis: The working memory hypothesis, the idea of the hippocampus as necessary for internal and external inhibitory processes as defined in Pavlov (1927), the idea of stimulus-response bond suppression or inhibition by the hippocampus, and the concept of inhibitory control of attention either through an unspecified mechanism (Gerbrandt, 1964) or through inhibitory efferent control of sensory reception (Douglas & Pribram, 1966). These ideas are highly similar and do not represent greatly divergent viewpoints. For example, the working memory functions of sorting for relevance and excluding the irrelevant are also functions of the attention control mechanisms of the Douglas-Pribram model. In the latter model, something very similar to stimulus-response bond inhibition could occur if the hippocampus acted to exclude those aspects of a stimulus which triggered the given response. The striking isomorphism of the Pavlovian and the Douglas-Pribram models on the behavioral determination level has already been discussed. Until such time as all of these ideas have been elaborated to the point where differential predictions can clearly be made, any decisions between them must remain a matter of personal taste.

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