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The Hippocampus and Its Role in Memory

Clinical Manifestations and Theoretical Considerations*

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INTRODUCTION

Loss of memory is a frequent symptom in patients seen by neurologists. It is very infrequent, however, to encounter a patient with severe memory loss who does not have associated impairment of other intellectual functions and whose clinical picture is not complicated by the presence of other neurologic signs and symptoms or by clouded or altered states of consciousness. Much research has been done on memory, but there is still much to be learned about it (Russell 1959; Young 1970). An analysis of the following case may give some insight into some of the problems associated with memory and impairment of it.

CASE REPORT

A patient was recently reported upon who had abruptly developed severe memory impairment without other symptoms or signs of neurologic involvement (DeJong, Itabashi and Olson 1969). This patient had a long history, and a family history of vascular disease. He had suffered his first coronary infarct at the age of 32 years. He had subsequently developed symptoms and signs suggestive of the Leriche syndrome. He entered the hospital at the age of 44 because of the recent onset of spells of faintness and vertigo with some of which he had associated diplopia. There were no significant abnormalities on the neurologic examination. There was mild arteriovenous nicking of the retinal vessels. An electrocardiogram showed evidence of previous anterior myocardial infarction and also possible recent myocardial ischemia. Plethysmography of the legs showed bilateral superficial femoral artery insufficiency. The serum lipoprotein electrophoretic pattern was that of hyperlipoproteinemia type II of Frederickson, Levy and Lees (1967). Because of the presence of microscopic hematuria, cystoscopy was carried out under barbiturate and nitrous oxide anesthesia.

The morning following the cystoscopy the patient complained of severe headache and observers noted a definite change in his personality, behavior and memory. He was confused and disoriented, and complained of inability to think. He denied having the symptoms for which he had come to the hospital, did not recognize his physicians, and was unable to find his room or the bathroom. The memory difficulty persisted, but no other neurologic abnormality was found. On intelligence testing he gave results within the normal range, but he performed poorly on subtests for information recall. Because no organic cause for the memory loss was found, the difficulty was thought to be psychogenic in origin and he was transferred to a psychiatric service. There he talked incessantly about his memory problems. He often missed his appointments because

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he could not remember the schedule or could not find the correct office. He consulted a card in order to recall his room number. The memory impairment seemed to have some relationship to the patient's emotional state. The deficit seemed to increase when he was "upset", and he often had marked difficulty remembering items and names that had a strong emotional element connected with them. He suffered a myocardial infarction and died 4 months after the onset of the memory difficulty.

At autopsy the patient was found to have a recent myocardial infarction and extensive atherosclerosis in the thoracic aorta and the iliac and vertebral arteries. On coronal section of the brain there were discrete bilateral infarcts of the hippocampi, greater in extent on the left side, where there was also involvement of the parahippocampal and fusiform gyri along the collateral fissure. These extended to the inferior lips of the calcarine fissures. On the right there was total destruction of the hippocampus except for the alveus; on the left there was also virtually complete destruction of the hippocampus with only focal sparing of the end plate, alveus and fimbria at different levels. The fornices were pale but not necrotic. The occipital lesions spared the primary visual cortex. The rest of the brain, including the amygdaloid nuclei, mammillary bodies and thalamus, was normal. All of the lesions showed an identical stage of necrosis consistent with an infarction that was several months old. The infarcts were in the territories of the perforating branches of the posterior cerebral arteries. These latter are the terminal branches of the basilar artery, and the symptoms for which the patient first sought medical attention were probably due to vascular insufficiency in the distribution of the vertebrobasilar arterial system. In spite of the absence of focal neurologic signs, particularly localizing ones, it can be assumed that the bilateral deep cerebral infarctions, with resulting permanent damage, occurred during a period of relative hypotension which accompanied the anesthesia.

DISCUSSION

Memory has been defined variously by laymen, neurologists, psychologists, and others. Webster (1970), as his first definition, states that it is "the power or process of reproducing or recalling what has been learned or retained". Dorland (1965) calls it "That mental faculty by which sensations, impressions, and ideas are recalled". Eccles (1966) has defined it as "that property of the nervous system whereby it is effective both in the storage and the retrieval of information". From a clinical point of view it is often, but not always, possible to differentiate between various categories of memory—retention and immediate recall, recent memory, and remote memory. The current discussion deals with memory as an intellectual process—that is the consciously bringing back to mind of that which one has once learned or known. Psychologically, and in its complete sense, however, memory also includes the retention, reproduction, and repetition of motor and behavioral activities that were once learned.

Memory loss is usually found in association with widespread disturbances of cerebral function. In the senile cerebral degenerations, for instance, and the presenile and other organic psychoses, memory loss may be the earliest and most distressing symptom, but there are always other evidences of mental impairment, which should be found if our search in sufficiently assiduous—decrease in intellectual capacity, loss of judgment and comprehension, lack of inhibition, emotional lability, etc. (Wells 1971). In the toxic and deficiency states there are associated lowering of consciousness, confusion, and disorientation. In Korsakoff's psychosis there are the associated confabulation and polyneuropathy, and in the Korsakoff–Wernicke syndrome, lowering of consciousness and cranial nerve dysfunctions (Victor, Adams and Collins 1971). In the post-traumatic (and associated retrograde) amnesias the memory loss affects only a circumscribed period of time or certain experiences, and a history of trauma, and of other post-traumatic sequelae, is usually available (Williams and Zangwill 1952). The memory loss following electroshock therapy and status epilepticus are well known (Symonds 1966). In postanoxic sequelae, and in those rare patients

who have survived a devastating encephalitis, the associated neurologic manifestations are legion (Drachman and Adams, 1962). The patho-anatomic involvement in all of these is quite extensive, and pathologic change is seen in many structures such as the temporal lobes, hippocampi, parahippocampal gyri, mammillary bodies, thalami, fornices, periventricular and periaqueductal gray matter, and others. Memory loss may be an early symptom in patients with brain tumors, especially those affecting the temporal lobes, the frontal lobes, or the mesial portions of the diencephalon. In such cases, too, the memory loss is only one part of the clinical picture, and there are usually associated neurologic signs and/or signs of increased intracranial pressure or disturbances of the state of consciousness. One must not overlook memory loss as a purely psychologic manifestation, and most cases of amnesia reported in the lay literature are entirely psychogenic or hysterical. Such was early thought to be of significance in this patient. Careful psychologic and psychiatric testing should, in most instances, clarify the etiology.

The hippocampal formation is a prominent structure on the medial aspect of the brain and is seen projecting from the floor and wall of the lateral ventricle. Embryologically and phylogenetically it has been studied in a wide range of vertebrate forms, and it appears in the dorsomedial hemisphere wall before the corpus callosum is developed (Crosby, Humphrey and Lauer 1962). With the development of the neopallial cortex and the appearance of a corpus callosum, it retreats from the dorsomedial wall of the hemisphere into the wall of the lateral ventricle. It is composed of the cornu ammonis, or Ammon's horn, and the dentate gyrus and the subiculum are often considered as being parts of it. It is separated by the hippocampal fissure from the hippocampal or parahippocampal gyrus. Beneath the ependyma lining the floor of the lateral ventricle there is a layer of myelinated fibers, the alveus. This becomes continuous with the fimbria along the medial border of the hippocampus. The fimbria is directed posteriorly and dorsally and is continued into the body of the fornix. This latter is the chief efferent path of the hippocampus. It discharges to, among other structures, the mammillary bodies, septal area, thalamus, hypothalamus, and midbrain tegmentum.

Although the hippocampal formation is a large structure, one of the most easily recognizable in the mammalian brain, and considerable information is available concerning its anatomic connections, relatively little is known about its functions. While it was originally considered to be a part of the olfactory system, it has become increasingly clear that in higher mammals it has only very indirect functional relations, if any, with the olfactory system, in contrast to former beliefs. Brodal in 1947 stated that recent physiologic experiments had yielded no support for the concept that the hippocampus has any important relations to the sense of smell in mammals. Clinical evidence as well has failed to show any relationship to the olfactory system. In developing mammals it does not parallel the development of olfactory functions. Animals with destruction of the hippocampus or section of the fornix bilaterally have no disorders of olfactory discrimination.

The hippocampus, along with the subcallosal, cingulate, and hippocampal gyri, make up the rhinencephalon or *limbic lobe*. The cytoarchitecture of these structures differs from that of the neocortex, and they have been said to have archi- or paleo-

cortices. Additional structures with similar architecture, and in close proximity, are the posterior orbital, insular, and temporal polar cortices. These, with underlying subcortical nuclei, including the amygdala, septal nuclei, preoptic area, hypothalamus, anterior thalamic nuclei, epithalamus, and parts of the basal ganglia, are said to constitute the limbic system. In 1937 Papez concluded that many of these structures, formerly considered to be concerned with olfaction, formed an anatomic substrate of the emotions, and play a part in the central control of emotional reactions, arousal, apathy, rage reactions, autonomic and visceral functions, sexual activity, and behavior. Localized lesions and localized stimulations bring about changes in the above functions, as well as behavioral changes that resemble those of psychomotor epilepsy, and seizure discharges from it spread to other parts of the limbic lobe and the neocortex.

Furthermore, the hippocampus, and doubtless its functions, are closely related to the parahippocampal gyrus, the temporal lobe and cortex, and the amygdala. These areas are closely interconnected by interneuron pathways. Moreover, because of their proximity to each other, they are often involved in a common lesion, clinically, or may be affected together in experimental and surgical stimulation and extirpation. In fact, most of the lesions and surgical resections of the temporal lobe, to be discussed below, also include the hippocampus. To confuse the matter even further, the terms hippocampus (or hippocampal formation) and hippocampal (or parahippocampal) gyrus are often used more or less synonymously or interchangeably in some contributions to the literature.

Sanger Brown and Schäfer (1888) were probably the first to describe an apparent memory loss in a monkey after temporal lobectomy. Von Bechterew (1900) described a patient with severe memory disturbances as well as apathy over a period of many years. At autopsy he was found to have softening of the uncus and hippocampus, as well as the underlying structures, bilaterally. Klüver and Bucy (1939) first called attention to the severe behavioral changes in monkeys following bilateral ablations of the temporal lobes, including removal of the uncus and almost the entire hippocampus. Memory loss was an important part of the syndrome of "psychic blindness" described by them. The monkeys were presented with the same objects on repeated occasions, but they would examine them as though seeing them for the first time. A similar syndrome in man was reported by Terzian and Ore (1955); there was marked loss of both recent and past memory.

It was observed clinically that profound memory loss, often with preservation of other intellectual functions, may appear following bilateral (and in a very few instances, unilateral) resection of the temporal lobe carried out for treatment of intractable psychotic states and temporal lobe epilepsy by Penfield and Baldwin (1952), Falconer, Hill, Meyer, Mitchell and Pond (1955), Walker (1957), and others. In most instances the resections have been quite widespread and have involved not only the medial portion of the temporal lobes, including the uncus and amygdala, but also the parahippocampal gyrus and hippocampus. Severe memory loss, especially for recent memory, has also been reported with resections more strictly limited to the hippocampal zone by Penfield and Milner (1958) and Scoville and Milner (1957). The latter, in reporting on the patients that they had studied following temporal lobectomy,

stated that memory loss occurred only after the resection was carried out sufficiently posterior to cause damage to portions of the anterior hippocampus and parahippocampal gyrus. They felt that the uncus and amygdala were not necessary for memory.

In almost all instances of memory loss following temporal lobectomy, the difficulty occurred only with bilateral temporal lobe lesions, although there have been some reports with unilateral resection, especially on the dominant side. Penfield and Milner (1958) reported on 2 cases with a persisting recent memory defect after removal of the left temporal lobe, but in both there was electroencephalographic (EEG) evidence of dysfunction of the opposite temporal lobe also. In 1957 Walker reported on 4 patients with unilateral temporal lobectomies for seizures who suffered severe impairment of memory, especially of recent memory. Of these, however, 1 did not develop his memory difficulty until 1 year after the temporal lobe resection; 1 showed intellectual impairment and could not be tested adequately; 1 had an anterior cerebral artery aneurysm with involvement of the septal area; and 1 had EEG evidence of abnormality in the opposite temporal lobe. Meyer and Yates (1955), and Meyer (1959), on the other hand, reported no intellectual or memory loss and only a moderate decrease in auditory verbal learning ability in 9 patients in whom the dominant temporal lobe had been removed. Of 34 patients with right temporal lobectomies who were studied by Serafetinides and Falconer (1962), 7 had persisting recent memory defects. Only 1 out of 47 patients with normal postoperative EEGs had a memory defect, whereas 6 out of the 7 with a spike focus discharge from the opposite temporal lobe, using sphenoidal electrodes, had memory deficits. Dimsdale, Logue and Piercy (1963) did report a case of persisting impairment of recent memory without dementia following right temporal lobectomy in a patient who, both preoperatively and postoperatively, had normal EEGs, pneumoencephalograms, and angiograms and whose clinical examination failed to show any evidence of a lesion in the opposite temporal lobe. In general, however, it has been apparent that by far the majority of cases in which a memory defect occurs with the unilateral lesion, there is some evidence that the contralateral temporal lobe is also damaged.

Loss of recent memory has also been reported following section of the fornix, which carries the majority of the efferent fibers from the hippocampus. Sweet, Talland and Ervin (1959) reported sectioning the anterior columns of the fornix in a 36-year-old woman during the removal of a third ventricle cyst. Postoperatively she exhibited a prolonged retrograde amnesia which gradually diminished to a period of several weeks, and a loss of recent memory. She also had loss of temporal orientation. On the other hand, Dandy (1933) reported no sequelae in those patients who recovered after removal of benign third ventricle tumors, in whom the surgical procedure included section of the fornix, and Cairns and Mosberg (1951) stated that there was no impairment of intelligence in 8 out of 9 survivors.

Spontaneously occurring cases of memory loss with lesions involving these structures are extremely rare. Von Bechterew's case has already been mentioned. Glees and Griffith (1952) reported the case of a 58-year-old woman who had had disorientation, agitation, and severe loss of memory, especially for recent events, for 15 years prior to her death. At autopsy there was symmetrical destruction of the hippocampus and parahippocampal and fusiform gyri bilaterally. The number of fibers in the fornix was

markedly reduced, but the mammillary bodies were said to be normal. A similar, but less well documented, case was described by Grünthal in 1947. A most significant report is one by Victor, Angevine, Mancall, and Fisher (1961), who described a patient with severe amnesia and visual field defects following occlusion of both posterior cerebral arteries. The hippocampal formations, fornices, and mammillary bodies as well as the medial surface of the occipital lobe were affected bilaterally.

Stimulation studies on humans have also shown suggestive evidence that the hippocampus may be involved in memory. It is known that irritation of the temporal lobe and electrical stimulation of this portion of the brain may both evoke memories. Electrical stimulation of the exposed temporal cortex at operation has been extensively used as a method of investigation by Penfield and his colleagues, and he has collected a valuable and unique series of observations (Penfield and Jasper 1954). Some of these have included the reproduction of past experiences. The cortex stimulated was usually the lateral and superior aspects of the temporal lobe, but medial aspects have also been stimulated; we do not know how often the hippocampus itself has been stimulated in these studies. Bickford (1964), using depth electrodes, reported periods of amnesia with "paralysis of recall' following hippocampal stimulation, and Brazier (1964) described a temporary and completely reversible block of recent memory with such stimulation; the memory loss was restricted to a period of recent experience, but long-term memory and ability for immediate recall were unimpaired. Feindel (1964), one of Penfield's associates, on the basis of his studies stated "Three main lines of evidence can be marshalled to confirm the role of the temporal lobe in memory mechanisms. The lateral cortex and the gray matter extending from the first temporal gyrus into the Sylvian fissure appear to be concerned with memory recall, as based on stimulation responses. The periamygdaloid region on stimulation evokes a blocking of memory recording, probably by virtue of after-discharge which flows into central regions and which can affect widespread cortical activity. Bilateral disturbance or excision of the medial temporal region has been shown to be associated with profound disturbance of recent memory so that learning and recall of recent information is severely reduced. The precise anatomical structures associated with this profound defect have not yet been clearly segregated, but the periamygdaloid region, the hippocampal gyri and the hippocampus itself appear to be most crucially involved". It is of interest that in some of Jackson's first cases of what he desbribed as "the uncinate group of fits" in which he reported automatisms, olfactory hallucinations, smacking movements of the tongue and lips, and "recollections or reminiscences", there were lesions of the medial portion of the temporal lobes, which must have involved the hippocampus also (Jackson and Beevor 1889).

In many of the earlier reports on the "pathology of epilepsy", much emphasis was placed on lesions in the Ammon's horn area. Earle, Baldwin and Penfield (1953) called attention to the frequent presence of "incisural sclerosis" in epilepsy, especially in patients with seizures of the temporal lobe of psychomotor type. This pathologic alteration is believed to be the result of herniation of the inferior mesial portion of the temporal lobe through the incisura of the tentorium at the time of birth; it is usually bilateral. The area of sclerosis usually, if not always, includes at least part of the hippocampal formation. In discussing Dr. Milner's presentation of 2 patients with recent

memory loss with unilateral hippocampal lesions, Penfield (1955) suggested that they might also have contralateral incisural sclerosis, and in the same discussion stated that the loss of recent memory in ageing might be due to arteriosclerotic changes in the hippocampal regions.

In many of the above-mentioned case reports "memory loss" is not further differentiated, and one would assume that both long-term memory and short-term memory were affected. Many of the patients were reported to show loss of retention and of remote, or long-term memory—a "retrograde amnesia". There was also, however, impairment of acquisition and of ability to learn, and many of authors have stressed especially the loss of recent memory (Penfield and Milner 1958; Scoville and Milner 1957; Walker 1957), and have stated that the major defect was in the loss of ability to record current experiences, and that past memory might be quite well preserved. Critical review of the reports, however, reveals that in the majority both recent and remote memory were affected, although not all tests for recent memory were similarly affected. This was also the case with the patient herein described. His immediate, recent, or short-term, memory seemed to be predominantly impaired, although there also appeared to be reduction of his distant, remote, or long-term memory. This may, of course, indicate that two different processes were taking place, both organic in nature, or two different processes, one organic and one psychogenic. Either the loss of long-term memory may have been a psychogenic amnesia, or the difficulty with recent memory may have been psychogenic, although it is doubtful that either was the case. Perhaps, however, this simultaneous impairment of these two types of memory is an important one, and further analysis of why both were affected may give a better understanding of the functions of the affected portions of the nervous system.

Drachman and his associates carried out some important studies in an attempt to document the clinical evidence linking memory deficits in man with bilateral lesions of the rhinencephalic structures. First, using monkeys with experimental lesions in these areas, which were later confirmed pathologically, Drachman and Ommaya (1964) found impairment of acquisition and loss of retention, but no impairment of short-term memory. They did dicuss, however, the difficulties in comparing human and animal studies. Drachman and Arbit (1966) found that patients with known or presumed bilateral lesions of the hippocampal regions had intermediate memory spans which were normal compared to a group of 20 control subjects. The patients, however, showed severe impairment in learning "supraspan" memoranda, even after multiple repetitions. They concluded that this indicated impairment of storage abilities in patients with bilateral hippocampal lesions, and that it is long-term rather than short-term memory which is impaired; what has been referred to as a loss of recent memory may be impaired acquisition and storage.

The exact role of the hippocampus in the memory process is not known. Green (1964) doubts that memories are stored in the hippocampus, but suggests that the amnesia which follows hippocampal lesions is due to disturbance of the incoming and outgoing pathways. Agranoff (1969) states that impulses which enter the brain are first directed to and converted into a short-term memory store. There is decay of a certain percentage of the short-term memories, and the remainder are transferred into a long-term store. It is the sum of the short-term and long-term memories which result in

performance. He postulates that the hippocampus is the structure which is important in the conversion of short-term to long-term memories, and that with lesions of the hippocampus there is a decrease or loss of such conversion. One might postulate further, however, that if the hippocampus is essential to conversion of short-term to long-term memories, it may also play a part in the registration and storage of short-term memories, and that these, as well as long-term memories, may be affected with hippocampal lesions.

An interesting observation in this case was the increase in memory defect when the patient was "upset"; the most pronounced loss of memory was for "emotionally charged" events and items. This led to the interpretation by many observers that the memory loss was on a psychogenic basis, and sodium amobarbital (Amytal®) interviews were carried out to find underlying emotional factors which might be of importance. It is probable that the hippocampus is not the primary center for the "storage" of memories, but rather a region for integration and sorting of information, for storage elsewhere. It also, however, as part of the limbic system, subserves emotions. One might speculate that the input of charged emotion and higher memory functions are incompatible, and that when the function of emotional expression predominates, memory is impaired.

This case documents further the growing body of evidence of the relationship of the hippocampus to memory. The involvement was more limited than in the previously reported cases of von Bechterew (1900), Glees and Griffith (1952), and Victor *et al.* (1961). The importance of the hippocampus in the mechanism of memory and recognition of the familiar is now quite well accepted. Usually, however, it is postulated that other parts of the nervous system must also be affected for disturbances of memory. Whitty (1962) suggested that neurons forming part of the limbic system, especially those in the hippocampus, mammillary bodies, and anterior thalamus, are essential for learning and the formation of new memories, whereas a cortical system of neurons in the temporal and parieto-occipital regions, probably of both the major and minor hemispheres, is essential for the storage and retrieval of memories. Barbizet (1963) has postulated that the hippocampus and the mammillary bodies play a dominant role in memorizing new material, whereas old memories require the integrity of various cortical and subcortical areas. Victor (1964), in a critical review of the amnestic syndrome in man and its anatomic basis, stated that the anatomy of memory is an extremely complicated matter, but it is generally acknowledged that the medial parts of the temporal lobes, specifically the hippocampal formations and their connections via the fornix, are of fundamental importance for learning and memory, but that loss of memory occurs only with bilateral lesions of the hippocampal formations. The hippocampus projects, via the fornix, to many structures other than the mammillary bodies, and the individual role of these various structures in the memory process is not fully understood. Detailed intellectual and behavioural studies of patients with lesions of the type that this patient had, should add to our knowledge of the functions of the hippocampus.

Memory is a very complex phenomenon, with multiple aspects and facets. The brain is an extremely complex structure with many connections, and various areas of the brain have either inhibitory or facilitatory control over other areas. There obviously

is no "center" for memory and perhaps no most important "center". The late Dr. Mackay (1955) once said that it is unwise to attempt to localize memory as a global function in any portion of the nervous system. Clinical observations and experimental studies, however, have shown that memory may be impaired with lesions in various areas of the brain, namely the temporal cortex, the parahippocampal cortex, the cingulate gyrus, the mammillary bodies and other hypothalamic structures, certain thalamic nuclei, the midbrain reticular formation, and also the hippocampi and their connections with other centers through the fornices. The latter do appear to be crucial for at least certain memory functions, and they may be involved with sparing of the uncus, amygdala, and anterior portion of the temporal lobe. It is entirely possible that memory is not localized in these structures or that these parts of the brain in any way form a "memory center", but only that these are sites where small lesions may have devastating effects on memory and learning.

SUMMARY

Using as the basis for discussion a case report of a patient who had developed severe memory impairment without other evidence of neurologic involvement following barbiturate and nitrous oxide anesthesia, and who was found to have bilateral infarcts involving the hippocampi and neighboring structures, the relationship of the hippocampus to memory is discussed. There have been a few other similar cases reported. Memory loss often follows bilateral temporal lobectomy, and even unilateral temporal lobectomy if section includes portions of the uncus, parahippocampal gyrus and hippocampus. Stimulation of the hippocampus also causes disturbances of memory. While there is no memory "center", and lesions of various portions of the nervous system may affect memory, the hippocampi appear to be crucial for certain memory functions, and small lesions in them may cause profound disturbances of memory and learning.

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