Ann. Rev. Neurosci. 1982. 5:241–273

THE NEUROPSYCHOLOGY OF HUMAN MEMORY*

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INTRODUCTION

The biology of memory is presently being investigated at a variety of levels from the cellular to the neuropsychological. The interdisciplinary nature of neuroscience has encouraged the belief that superficially dissimilar phenomena—e.g. collateral sprouting, receptor adaptations, synaptic depression and facilitation, dendritic growth in response to enriched environment, and recovery of function after brain injury—are all potentially relevant to questions about memory because they all reflect the nervous system's capacity for plasticity. Yet, a satisfying account of the biology of memory must include not only information about the details of synaptic change but also a description of the learning processes and memory systems whose neurobiological mechanisms we wish to understand, plus information about how memory is organized in the brain, how memory changes with time, and which brain regions are involved.

A favorable strategy for addressing these questions has been to study amnesia. Most often, disorders of memory occur in the context of impairment in other aspects of intellectual function, as in depression or dementia. Nonetheless, amnesia can occur as a relatively circumscribed disorder in the absence of other cognitive impairment. As in many areas of biology where disorders of function have taught us about normal function, so the analysis of memory disorders can provide insights into the structure and organiza-

tion of normal memory (for other recent reviews, see Piercy 1977, Weiskrantz 1978, Squire & Cohen 1982).

This review considers four aspects of memory and amnesia—*anterograde amnesia* or loss of memory for events that occurred after the onset of amnesia, *retrograde amnesia* or loss of premorbid memory, *preserved learning capacity,* and the *anatomy of amnesia.* Each of these topics is organized around the specific issues that have guided the past decade of experimental work, with the intention of summarizing what is presently known about the organization of memory and its neurological substrate.

THE AMNESIAS

The globally amnesic patient can appear normal to casual observation. Such a patient may have normal intellectual capacity, normal digit span and intact social skills, and may retain knowledge acquired in early life. The defect lies in acquiring new memories and in recalling some memories that had been acquired prior to becoming amnesic. This defect often occurs in the absence of confabulation or confusion and with awareness by the patient of his condition. Note that the amnesic syndrome has no connection to hysterical memory loss of psychogenic orgin. By far the most frequently studied example is found in Korsakoff's syndrome. First described in 1887 (Korsakoff 1887), this syndrome has been studied extensively during the past one hundred years (Talland 1965, Victor et al 1971, Butters & Cermak 1980). The disease develops after chronic alcohol abuse and is characterized by symmetrical brain lesions along the walls of the third and fourth ventricles as well as in the cerebellum and cerebral cortex. After the acute stage has passed, the patient with Korsakoff syndrome is alert and responsive and has normal intellectual capacity, as assessed by conventional tests. The disease produces a spectrum of cognitive deficits, but amnesia occurs out of proportion to other neuropsychological findings.

Additional information about global amnesia has come from the rare individual case in which amnesia occurs as a strikingly circumscribed entity. The best-known and most thoroughly studied of these is case H. M. (Scoville & Milner 1957). In 1953, H. M. sustained bilateral resection of the medial temporal region in an attempt to relieve severe and intractable epilepsy. The resection included the anterior two-thirds of the hippocampal formation, parahippocampal gyrus, amygdala, and uncus. Following surgery, H. M. exhibited a profound amnesic syndrome in the absence of any detectable change in general intellectual ability. H. M. has been carefully studied by Brenda Milner and her colleagues at the Montreal Neurological Institute, and the findings from this case alone have provided an enormous amount of information about memory. A second well-studied patient is case

N. A. (Teuber et al 1968, Kaushall et al 1981), who became amnesic in 1960 following a penetrating brain injury with a miniature fencing foil. Recent CT scans have identified a lesion in the region of the left dorsomedial thalamic nucleus (Squire & Moore 1979). Consistent with these radiographic findings, neuropsychological studies have demonstrated that the amnesia is more pronounced for verbal material than for nonverbal material (Teuber et al 1968, Squire & Slater 1978). For example, he forgets lists of words and connected prose more readily than faces or spatial locations. In this sense, N. A.'s memory deficit is material-specific, rather than global (Milner 1968). Like the global amnesia of H. M., N. A.'s deficit occurs in a bright individual (N. A.'s IQ is 124) without notable neuropsychological findings other than amnesia.

A final type of global amnesia is that produced by bilateral electroconvulsive therapy (ECT) (Squire 1981a). ECT is sometimes prescribed for the treatment of depressive illness, and amnesia is its prominent side effect. Since ECT is a scheduled event, it is unique among the better studied amnesias because it provides an opportunity to use each patient as his own control in before-and-after studies. The amnesia recovers to some extent after each treatment in a series and cumulates across treatments. Treatments are usually scheduled every other day, three times a week, and a series of treatments typically consists of six to twelve treatments. By one hour after treatment, amnesia appears as a rather circumscribed deficit in the absence of gross confusion or general intellectual impairment.

The amnesias outlined above do not of course exhaust the list of causes or types of amnesia. For example, amnesia can also occur after head injury, anoxia, encephalitis, tumor, or vascular accident. But the amnesias described above have been studied the most extensively in recent years, particularly from the point of view of the neuropsychology of memory.

ANTEROGRADE AMNESIA

Amnesia as a Non-Unitary Disorder

Comparison of different amnesias clearly indicates that they do not all take the same form. Moreover, some behavioral deficits exhibited by amnesic patients have no necessary relationship to amnesia at all. This point can be made most clearly by comparing the Korsakoff syndrome to other examples of amnesia. Thus, patients with Korsakoff syndrome have cognitive and other clinical deficits not shared by other amnesic groups. These individuals commonly exhibit apathy, blandness, lethargic indifference, or vacuity of expression, loss of initiative, placidity (Talland 1965, pp. 19, 29). Yet there is no necessary relationship between amnesia and these features. Case N. A., for example, is energetic and alert, easily initiates social contact, and

interacts with people in an agreeable, friendly way (Kaushall et al 1981). Zangwill also has commented on the very different appearance of the Korsakoff syndrome in comparison to the more "pure amnesic syndromes . . . [possibly] involving the hippocampal region" (Zangwill 1977). Thus, the patient with Korsakoff syndrome performs poorly on a variety of cognitive tests, such as those requiring rapid switching of strategies (Talland 1965, Oscar-Berman 1973, Glosser et al 1976, Butters & Cermak 1980). Case H. M.'s amnesia, by comparison, is well circumscribed, and he performs well on many such tests (Milner 1963, Milner et al 1968).

A particularly clear example of how the memory impairment associated with the Korsakoff syndrome is different from other examples of amnesia comes from a study of proactive interference. Proactive interference (PI) refers to the interfering effects of having learned a first task on the learning of a second task. Like normal subjects, patients with Korsakoff syndrome exhibit a gradual decline in recall due to PI when learning successive groups of words that all belong to the same category (e.g. animal names). Normal subjects, but not patients with Korsakoff syndrome, exhibit an improvement in recall (or release from PI) when words are presented that belong to a new category (e.g. vegetable names) (Cermak et al 1974).

Recently, these results have been placed in clearer perspective by the finding that failure to release from PI is a sign of frontal lobe dysfunction, with no obligatory link to amnesia (Moscovitch 1981). Patients with material-specific memory disorders (Milner 1968), who had sustained left or right unilateral temporal lobectomy, exhibited normal release from proactive inhibition. Moreover, patients who had sustained surgical removal of portions of the frontal lobe, and who were not amnesic, failed to release from proactive inhibition. These findings suggest that frontal lobe dysfunction determines some of the features of the Korsakoff syndrome. They also indicate the value of comparisons between amnesic groups for understanding the nature of memory dysfunction. Clearly, generalizations about amnesia or the amnesic syndrome are not appropriate when speaking about one kind of amnesia.

A final example that makes the same point comes from studies of information-encoding by patients with Korsakoff syndrome, case N. A., and patients receiving ECT (Cermak & Reale 1978, Wetzel & Squire 1980). An orientation procedure was employed to assess how well these patients were capable of three kinds of encoding (Craik & Tulving 1975). By this procedure, encoding during learning is controlled by the experimenter through orienting questions that direct the subject's attention to the superficial appearance of a word, to its sound, or to the semantic category to which it belongs. On such a task, normal subjects exhibit superior recall of semantically encoded words. Case N. A. and patients receiving ECT exhibited the

normal superiority of recall for words that had been encoded semantically; and their retention scores, though considerably lower than normal, paralleled the normal pattern of performance. Patients with Korsakoff syndrome failed to exhibit superior retention of semantically encoded words.

These findings are relevant to ideas about the nature of the disorder in amnesia. For example, theories that emphasize a semantic encoding deficit (e.g. Butters & Cermak 1980) seem applicable only to the Korsakoff syndrome. Since N. A.'s amnesia (which did not include this semantic encoding deficit) is thought to result from damage in the region of the dorsomedial thalamic nucleus (Squire & Moore 1979), and since this nucleus is also prominent in the neuropathology of Korsakoff syndrome (Victor et al 1971), some characteristics of the amnesia exhibited in Korsakoff syndrome must reflect lesions outside of the dorsal thalamic region. The possible contribution of frontal lobe dysfunction to the semantic encoding deficit described above has not been evaluated, but it is well known that the frontal lobes have a role in the maintenance and flexible use of central "sets" (Teuber 1964, Luria 1960). The term "set" refers to a temporary domination of behavior by a particular strategy or hypothesis or by the direction of attention to a particular aspect of the environment.

The evidence reviewed so far has tended to place the Korsakoff syndrome apart from other types of amnesia, primarily because this syndrome is associated with various cognitive deficits that occur together with amnesia and in some cases seem to determine its character. Thus, one could suppose that a common core of amnesia does exist in all instances of the amnesic syndrome, and that this core can sometimes be obscured by the effects of additional lesions and superimposed cognitive deficits. In the next section, however, I suggest that the basic amnesic disorder can take different forms.

Two Forms of Amnesia

Recent studies of forgetting provide strong evidence that there are at least two distinct amnesic syndromes and that diencephalic amnesia and bitemporal amnesia are fundamentally different. This idea was first advanced by Lhermitte & Signoret (1972) and is supported by recent findings (Huppert & Piercy 1978, 1979). In brief, these studies used a procedure designed to minimize the problem of comparing forgetting rates in two groups that already differ in levels of initial learning. For learning, patients viewed 120 colored slides. Retention was assessed by a yes/no recognition procedure at three different intervals after learning (10 min, 1 d, and 7 d). Forty new slides and 40 of the original slides were presented at each interval. To equate retention at 10 min after learning, amnesic patients were given longer to view the slides during learning than control subjects ($4x$ or $8x$ for Kor-

sakoff patients, 15x for case H. M.). Having equated performance at 10 min after learning, it was then possible to ask whether the rates of forgetting during the next seven days were normal or abnormal. Huppert & Piercy found that patients with Korsakoff syndrome exhibited a normal rate of forgetting for material they were able to learn, whereas H. M. exhibited an abnormally rapid rate of forgetting. Yet, H. M. required more exposure during learning to raise his 10 min retention score to control levels than did the Korsakoff patients, presumably because his amnesia was more severe than that of the Korsakoff patients. Accordingly, one might worry that severity of amnesia is related to forgetting rate.

This possibility, however, has been ruled out by more recent work that extends the analysis of forgetting rates to case N. A., patients receiving ECT, and to the San Diego Korsakoff population (Squire 1981b). All amnesic patients viewed the material to be learned for a total of 8 sec. Despite similarity in the level of retention achieved at 10 min after learning, Korsakoff patients and case N. A. exhibited a normal rate of forgetting during the next 32 hr, and patients receiving ECT forgot at an abnormally rapid rate. These findings support the idea that diencephalic amnesia, of which Korsakoff patients and case N. A. are clear examples, is characterized by a normal rate of forgetting. By contrast, bitemporal amnesia of which H. M. is an example, and the amnesia associated with ECT are characterized by rapid forgetting. Although it is obviously not possible to speak with certainty about the anatomy of the amnesia associated with bilateral ECT, the sensitivity of the hippocampal formation to seizures suggest that this amnesia might primarily reflect medial temporal dysfunction (Inglis 1970).

SUMMARY The experimental study of amnesia has raised the possibility that diencephalic and bitemporal amnesia are distinct entities, and supports the related idea that these two brain regions contribute in different ways to normal memory functions. Patients with Korsakoff syndrome and case N. A. appear to belong to one category, and case H. M. and patients receiving ECT belong to another. This conclusion seems particularly strong in view of the fact that patients with Korsakoff syndrome, who have a variety of cognitive deficits in addition to amnesia, nevertheless had a normal forgetting rate; whereas H. M. and patients receiving ECT, who exhibit rather circumscribed amnesias by comparison, had abnormal forgetting rates. In addition, the Korsakoff syndrome appears to include features not shared by these other examples of amnesia. These ideas support a scheme for classifying amnesia based on behavior and on the presumed nature of the underlying neuropathology, a proposal that can be rigorously tested as additional examples of amnesia are submitted to an analysis of forgetting and as animal

models of human global amnesia are perfected (Thompson 1981, Mishkin et al 1981, Squire & Zola-Morgan 1982). This discussion of how amnesias are similar and different sets the stage for considering the nature of the underlying deficit and the role of the affected brain regions in normal memory functions. I next consider these issues.

The Nature of the Deficit

Understanding the basic memory defect in amnesia is fundamental to the neurology of memory. Yet, after decades of experimental work, disagreement remains about how best to characterize it. In the next section I consider some reasons that these matters have been so hard to settle and I summarize the current literature.

BACKGROUND: STORAGE VS RETRIEVAL Usually amnesia has been considered to reflect a disorder in some particular stage of information processing, such as storage, consolidation, or retrieval. This kind of analysis has been applied to amnesia in man (Squire 1980a, Wicklegren 1979) and in laboratory animals (Miller & Springer 1973, Gold & King 1974). Both efforts, following relatively separate courses, have become mired in the same polarization of opinion: Is amnesia a deficit of storage or retrieval?

This issue is connected in turn to a long-standing debate about normal brain function: Is material permanently stored in memory such that normal forgetting reflects only a change in accessibility or retrievability, or is forgetting actually associated with loss of information from the brain? Commitment to the idea of permanent memory storage leads quite naturally to thinking about memory dysfunction in terms of retrieval failure. Popular ideas about hypnosis, repression, and psychoanalytic theory have apparently led the majority of individuals to believe that most, if not all, memories are stored permanently (Loftus & Loftus 1980). This idea has deep historical roots in Freud's view that "in mental life nothing which has once been formed can perish" and that forgetting is motivated in part by repression (Freud 1930).

In fact, it is simply not yet possible to determine directly whether the neural substrate of mammalian information storage is maintained permanently or whether it dissipates with time. Disagreement will probably remain about this fundamental issue until decisive biological evidence can be obtained. Nevertheless, it is worth pointing out that the bias for considering representation of memory in the brain to be permanent has been reviewed recently from the perspective of cognitive psychology (Loftus & Loftus 1980), with the conclusion that there are no psychological data that would require such an idea. The common experience that we have available in memory far more than we are able to recall on any particular occasion

should not convince us that all past experiences are permanently represented in storage.

The issue need not be so simple as whether a particular past experience is or is not in memory storage. Memory of a particular face, word, or event could dissipate from storage but could nevertheless influence behavior in a less literal, but long-lasting way by virtue of having been incorporated into more generic representations or schemata (Bartlett 1932, Rumelhart & Norman 1978). Schemata are knowledge structures that constitute procedures for interpreting new information and operating in the world. An experience of a particular face might leave no neural trace that would aid later recognition of the same face; yet it could tune or elaborate neural mechanisms (schemata) specialized for facial recognition.

Not only does there not seem to be any compelling reason for supposing that memory storage in the brain is always permanent, but available information about the nervous system's capacity for plasticity makes it easy to envision ways that some information could be erased or absorbed with time. For example, areas of mammalian cortex are capable of considerable reorganization in dendritic architecture as a function of experience during adulthood (Greenough et al 1979, Juraska et al 1980), and in man growth of these elements normally continues throughout life (Buell & Coleman 1979). During development, where synaptic reorganization has been best studied, growth and elimination of synaptic elements appear to follow a principle of competition, whereby loss of elements leads to an increase in innervation by surviving elements (Purves & Lichtman 1980). This principle might also apply to the changes produced after visual deprivation, and to certain aspects of memory and forgetting (Squire & Schlapfer 1981). These dynamic features of the nervous system provide a way of understanding how the neural substrates of information could change with time. Finally, and perhaps most relevant, in invertebrates, where the cellular correlates of information storage for simple forms of behavioral plasticity can be investigated rather directly, the relevant neural changes gradually disappear over a period of days and weeks (Kandel 1976).

Yet the difficulty in discovering the nature of amnesia reflects more than an historic debate about the permanence of memory storage; it reflects confusion over the use of terms like "storage" and "retrieval." Consider the problem of distinguishing a storage deficit from a retrieval deficit. Any deficit in the initial storage of information will necessarily result in a deficit in its retrieval. Moreover, unless a deficit can be fully reversed, any improvement in recall after special cueing or prompting procedures can be interpreted either as evidence for the reduction of a retrieval deficit or as evidence for incompletely stored information that can be expressed better when prompts or cues are provided. Notwithstanding these difficulties,

some progress has been made in understanding amnesia by experiments framed around storage and retrieval issues.

RETRIEVAL EXPLANATIONS The view that amnesia might reflect a deficit in retrieval of information that had been adequately stored seems to have developed as a way of understanding two prominent features of amnesia:

1. A variety of cues and other techniques seem remarkably effective in eliciting otherwise unavailable information from amnesic patients.
2. When recalling successive lists of words, many amnesic patients make intrusion errors, i.e. they produce words presented on previous lists, directly demonstrating some storage of recent information.

Facilitatory effects on the retention of amnesic patients have been demonstrated with a variety of techniques, including fragments of pictures or words, the initial letters of words, yes-no recognition, and two-choice recognition. Many of these procedures prove to be very effective in improving the performance of amnesic patients. Yet, the critical issue is not whether performance can be improved at all by such techniques but whether they disproportionately improve the performance of amnesic patients, or are simply effective ways to elicit information from all subjects, amnesic patients and normal subjects alike.

The evidence suggests that cues improve the performance of all subjects (Squire 1980a, Squire & Cohen 1982). Tests based on fragmented drawings have been given to H. M. (Milner et al 1968), and tests involving either fragmented drawings, fragmented words, or the initial letters of words have been given to patients with Korsakoff syndrome (Warrington & Weiskrantz 1968, Weiskrantz & Warrington 1970). These patients exhibited considerable retention over intervals of one hour or more, but nevertheless failed to attain the level of performance exhibited by control subjects. The control subjects also benefitted from these cues and maintained a marked advantage over the amnesic patients.

In verbal learning tests, patients receiving bilateral ECT exhibited a marked impairment in retention even when tested by procedures known to benefit performance: yes-no recognition, two-choice recognition, or cueing by the initial three letters of a word (Squire et al 1978). In addition, case N. A. improved his recall for past public events when his task was to discriminate true and false statements about these events (Squire & Slater 1977). But control subjects improved also and maintained their advantage over him. Thus, recognition is easier than recall for amnesic patients as well as for controls. "Like other men and women [amnesics] too are more likely to succeed in recognition than in unaided recall, but in all tests of memory

their capacity and reliability are abnormally small" (Talland 1965, p. 231). Taken together, the results with cues of various types provide no basis for supposing that amnesia reflects a failure to retrieve information that is adequately stored.

Another body of work sometimes taken in support of a retrieval explanation of amnesia concerns the finding that amnesic patients, when trying to recall a list of words, sometimes produce words learned on previous lists. Originally, this finding had been interpreted in the context of a retrieval explanation of amnesia to mean that response competition at the time of retrieval interferes with performance (Warrington & Weiskrantz 1974). However, this view has encountered difficulties and is now regarded as inadequate (Warrington & Weiskrantz 1978). For example, for patients with Korsakoff syndrome, retention scores and frequency of intrusions from a just learned list of words can vary independently of each other (Kinsbourne & Winocur 1980). Whatever the correct interpretation of intrusion errors, it should be emphasized that the study of these errors has been limited to the Korsakoff syndrome. Since patients with Korsakoff syndrome have cognitive deficits superimposed on amnesia, including symptoms of frontal lobe dysfunction that affect their performance on some memory tests (Moscovitch 1981), it is reasonable to wonder how typical intrusion errors are in amnesia. Moreover, since frontal lobe damage can cause perseverative errors (Milner 1963), questions can be raised even in the case of the Korsakoff syndrome as to whether intrusion errors constitute a part of the amnesia or reflect superimposed frontal lobe pathology.

STORAGE OR CONSOLIDATION EXPLANATIONS Another body of work has suggested that amnesia might reflect a deficit of information input or retention such that memory is not encoded normally during learning or is not consolidated or elaborated normally with the passage of time. One hypothesis, applied to the Korsakoff syndrome, is that amnesia reflects an encoding deficit (Butters & Cermak 1980). This view holds that the patient with Korsakoff syndrome has difficulty engaging in deeper (e.g. semantic) levels of information processing and as a result develops a representation of information based on superficial analysis.

Although patients with Korsakoff syndrome can differ from normal subjects, and even from other amnesic patients, with respect to their ability to use semantic information (Wetzel & Squire 1980, Cermak & Reale 1978, Wetzel & Squire 1981), it is also clear that such a deficit does not always appear, especially when the task is simplified (Cermak & Reale 1978, Mayes et al 1978, Mayes et al 1980). The results of information-encoding studies thus provide a mixed picture of the abilities of the Korsakoff patient. In any case, Korsakoff syndrome affects the speed and efficiency of information

processing as measured by divided attention and concept formation tasks (Glosser et al 1976, Oscar-Berman 1973)—cognitive deficits that could be expected to affect the ability to register information in a normal way. These findings and others have led Huppert & Piercy (1978) to argue compellingly that the Korsakoff syndrome involves at least a deficit in an early stage of information processing.

In addition to an encoding deficit, recent studies also raise the possibility that patients with Korsakoff syndrome in particular might also have cognitive deficits that could affect their ability to reconstruct information from memory in some circumstances. In one study, patients exhibited impaired retrieval from semantic memory (Cermak et al 1978). In a second study, patients exhibited impaired memory search strategies (Cermak et al 1980). These findings complicate attempts to define the deficit in Korsakoff syndrome in any simple way. They could have some specific cognitive deficit that affects both encoding and retrieval, as suggested by Kinsbourne & Winocur (1980), or their encoding and reconstructive deficits could be separate disorders.

Although the bulk of experimental work on anterograde amnesia has involved the Korsakoff syndrome, useful information about the nature of the deficit has also come from study of case H. M., case N. A., and patients receiving bilateral ECT. Whereas work with the Korsakoff syndrome has identified deficits in information-encoding that selectively interfere with deeper levels of processing, and possibly with the reconstruction of information, study of H. M. and patients receiving ECT has suggested that their amnesia reflects a deficit limited to the formation of new memory.

This view can be illustrated by a study of anterograde amnesia and memory for temporal order (Squire et al 1981). Amnesic patients are frequently confused about when an event occurred, although they might remember something about the event itself. This could mean that information about temporal order was represented weakly in storage, or that it was stored but particularly difficult to retrieve. In the study, case N. A. and ECT patients were tested after a short learning-retention interval. Control subjects were tested at various learning-retention intervals to determine when in the course of normal forgetting they were as poor as the patients at remembering two lists of 12 simple sentences. At this stage of forgetting amnesic patients were no worse than the control subjects at remembering whether sentences belonged to the first or second list. The same kind of result has been obtained for partial information (Squire et al 1978, Mortensen 1980), retention of semantically encoded words (Wetzel & Squire 1980), and cued recall of words (Wetzel & Squire 1981). In all cases the pattern of performance exhibited by amnesic patients (N. A. or patients receiving ECT) was recapitulated by normal subjects during the course of

normal forgetting. These results seem easiest to understand by supposing that these amnesias result in a weak representation in memory. A retrieval explanation is not needed to understand such results, except in the sense that such an explanation would apply to normal forgetting.

SUMMARY This consideration of the nature of anterograde amnesia was begun with the demonstration that there appear to be two classes of amnesia —one associated with a normal rate of forgetting and one associated with an abnormally rapid rate of forgetting. These two forms of amnesia would appear to require different explanations to account for the underlying disorder. The evidence just reviewed is consistent with the proposal that diencephalic amnesia reflects a deficit in the initial encoding of information, together with a normal retentive ability for information that can be acquired. In this respect the two kinds of diencephalic amnesia considered here, case N. A. and the Korsakoff patient, are similar. However, the comparatively widespread neuropathology of Korsakoff syndrome may be responsible for two features of the syndrome not observed in case N. A. and which seem to set the Korsakoff syndrome apart from some of the other amnesias:

1. A qualitative deficit in encoding that affects deeper, semantic, more elaborative aspects of information processing.
2. Reconstructive deficits and an extensive, possibly related, impairment in remote memory (Squire & Cohen 1981, Cohen & Squire 1981).

Patients receiving ECT and case H. M., who exhibit an abnormally rapid rate of forgetting, may be deficient in post-encoding processes involved in the consolidation or elaboration of memory. This idea was put forward several years ago to account for H. M.'s amnesia (Milner 1966). If a system involved in such a process were damaged, it seems reasonable that the deficit would be larger with an increasing learning-retention interval. This view of the amnesias, derived from analysis of anterograde amnesia, emphasizes a deficiency in initial registration or consolidation rather than in retrieval. Even stronger support for this view comes from study of retrograde amnesia: the loss of memory for events that occurred prior to the onset of amnesia.

RETROGRADE AMNESIA AND REMOTE MEMORY IMPAIRMENT

As recently as the early 1970s, opinion was divided about the nature of retrograde amnesia. On the one hand, clinical descriptions of case H. M. had consistently stated that this individual exhibits a brief retrograde

amnesia covering a period of perhaps 1 to 3 yr prior to the onset of his amnesia in 1953 (Scoville & Milner 1957, Milner 1966). Such clinical descriptions are not unusual, having been recorded for two other patients who sustained medial temporal resections (Penfield & Milner 1958) and for patients experiencing severe head injury (Russell & Nathan 1946). On the other hand, the first formal assessment of remote memory functions in amnesia, involving a mixed group of three Korsakoff patients and two other patients, revealed an extensive remote memory impairment affecting the entire period of time covered by the test, 1930–1970 (Sanders & Warrington 1971). These two views of retrograde amnesia turn out to be reconcilable in that they apply to etiologically distinct forms of the amnesic syndrome.

Premorbid vs Postmorbid Memory: Cases H. M. and N. A.

Formal testing of remote memory in two well-circumscribed cases of chronic memory dysfunction (case H. M. and case N. A.) has demonstrated that premorbid memory can be less affected than postmorbid memory and has confirmed clinical descriptions of these cases. H. M. performed as well as control subjects in recognizing famous faces from his premorbid period, 1920–1950, but identified fewer than 20% of the faces of individuals who became prominent after his surgery in 1953 (Marslen-Wilson & Teuber 1975). The status of N. A.'s remote memory has been evaluated with tests of past public events, former one-season television programs, and famous faces (Squire & Slater 1978, Cohen & Squire 1981). As assessed by six of seven tests, his remote memory appears unaffected for the period before his accident in 1960.

Brief Retrograde Amnesia: Temporally Limited Retrograde Amnesia

Until recently, the idea that retrograde amnesia could affect memories acquired as much as a few years previously rested entirely on clinical impressions of the sort described above. There has even been reason to wonder about the accuracy of these impressions. First, the findings of Sanders & Warrington (1971) raised the possibility that when retrograde amnesia does occur it is extensive rather than temporally limited. Second, a larger literature concerning experimental amnesia in laboratory animals had suggested that graded retrograde amnesia is typically brief (minutes or hours) and that long-term memory is rather invulnerable to amnesia (McGaugh & Herz 1972, Squire 1975). Accordingly, in trying to understand the clinical descriptions, some forcibly argued that reports of temporally limited retrograde amnesia extending across a year or more might be explained by sampling bias (Coons & Miller 1960). When interviewing a patient about his past memories, questions about remote events tend to be

more general and to cover a broader period of time than questions about recent events. Loss of memory for recent events is therefore easier to detect than loss of memory for more remote events.

A series of studies of patients receiving bilateral ECT, using specially designed tests based on former one-season television programs (Squire & Slater 1975, Squire & Fox 1981), has established that temporally limited retrograde amnesia is real and not an artifact of sampling bias. Patients were tested prior to the first treatment of their series and then again an hour or longer after the fifth treatment. Before ECT, patients performed similarly to control subjects. After ECT, memory was selectively affected for events that occurred just a few years prior to ECT but was normal for events that occurred prior to that time (Squire et al 1975, Squire et al 1976, Squire & Cohen 1979). A temporally limited retrograde amnesia has also been demonstrated using a test that asked patients to recall details about past public events (Cohen & Squire 1981). These retrograde amnesias gradually resolve during the months following treatment (Squire et al 1981). These findings, as well as those cases in which temporally limited retrograde amnesia is not observed following ECT, are considered more fully elsewhere (Cohen & Squire 1981).

These findings have interesting implications for the neuropsychology of memory. That memory can be lost for events of the past one to two years without affecting more remote memories has been taken as confirmation of Ribot's Law, that in the dissolution of memory the "new perishes before the old" (Ribot 1882). This finding also implies a normal process by which memory gradually becomes more resistant to disruption with the passage of time.

This phenomenon of increasing resistance could constitute the basis for gradual reorganization and restructuring in memory (Norman & Rumelhart 1975) and for the development of schemata (Bartlett 1932) that have been suggested to appear in normal memory with the passage of time. These considerations suggest that there develops gradually after learning a representation of the original experience that has lost detail through forgetting but that has become reorganized, schematized, and more resistant to disruption. Freud also proposed a relationship between forgetting and constructive changes in the representation of information. "Normal forgetting takes place by way of condensation. In this way it becomes the basis for the formation of concepts" (Freud 1901).

Little or nothing is known about the neurobiological events that might underlie these gradual changes in the development of memory. The nervous system is capable of gradual morphological change in response to rearing in enriched environments or to daily maze training (Greenough et al 1979, Juraska et al 1980, Rosenzweig 1979, Bennett et al 1979). The relationship

between forgetting and resistance is formally similar to the competition that can be observed during development of the nervous system (Purves & Lichtman 1980). In the case of development, as inputs to a cell are eliminated, the remaining inputs increase their influence on that cell. In the case of memory, as some information is forgotten, the remainder becomes more resistant to disruption.

Another implication of these findings is that permanent memory storage normally occurs outside the brain regions affected in amnesia. It appears that these brain regions constitute an essential neuronanatomical substrate for the formation of new memories and for their maintenance and elaboration after learning. The finding with objective tests that temporally limited retrograde amnesia can cover a time span of a few years also corroborates clinical impressions that case H. M. has retrograde amnesia for one to three years prior to his surgery. Taken together, these observations suggest that the medial temporal region plays a role in the development and consolidation of memory and that this role can continue for up to a few years after initial learning.

The findings with ECT, and the facts of brief retrograde amnesia in general, speak directly to questions about the nature of amnesia, as just reviewed in the context of anterograde amnesia. The marked discontinuity between premorbid and postmorbid memory, noted for cases H. M. and N. A., and the finding that the retrograde amnesia associated with ECT can be temporally limited, provide strong evidence against a general retrieval interpretation of these amnesias. A retrieval deficit should involve memory for all past events and not just memory for events that have occurred recently. Thus, for case H. M., case N. A., and the amnesia associated with ECT, the experimental facts lead to the consistent view that these amnesias reflect a deficit in the establishment and elaboration of memory.

It should be noted that retrieval explanations of amnesia (e.g. Warrington & Weiskrantz 1970, Kinsbourne & Wood 1975) derive largely from study of patients with Korsakoff syndrome whose anterograde amnesia is different in certain ways from that of other amnesic patients. The next section illustrates that, unlike the other amnesic patients considered here, patients with Korsakoff syndrome also exhibit an extensive impairment of remote memory.

Extensive Remote Memory Impairment: The Korsakoff Syndrome

Beginning with the seminal study of Sanders & Warrington (1971) demonstrating that amnesia can affect a large portion of remote memory, the status of remote memory in the Korsakoff syndrome has come to be rather well understood. Patients with Korsakoff syndrome exhibit a severe and exten-

sive impairment of remote memory that affects most of their adult lives. This impairment is temporally graded, affecting memory of recent periods of time to a greater extent than more remote periods, and has been consistently demonstrated in different patient populations using a variety of remote memory tests (Marslen-Wilson & Teuber 1975, Seltzer & Benson 1974, Albert et al 1979, Cohen & Squire 1981, Squire & Cohen 1981, Meudell et al 1980).

In considering this deficit, the term "remote memory impairment" is preferable to "retrograde amnesia." The Korsakoff syndrome develops gradually so that it is difficult to know what portion of memory for past events reflects anterograde amnesia and what portion reflects retrograde amnesia. Nevertheless, available information suggests how the combined effects of anterograde and retrograde amnesia might explain the remote memory findings. Anterograde amnesia may help to understand the graded aspect of the impairment. That chronic alcoholic patients have information-processing deficits (Ryan et al 1980, Parker & Noble 1977) and that they exhibit impairment on the more recent questions of remote memory tests (Cohen & Squire 1981, Albert et al 1980) suggest that with continued drinking alcoholics should gradually lose ground to nonalcoholic control subjects with respect to their ability to recall recent public events. Accordingly, after years of alcohol abuse the patient eventually diagnosed as having Korsakoff syndrome would be expected to demonstrate an amnesia for public events that is more severe for recent events than for remote events. By this view the gradient of remote memory impairment exhibited in Korsakoff syndrome reflects progressive anterograde amnesia.

The presence of certain cognitive deficits in Korsakoff syndrome might explain the extensiveness of the remote memory impairment. These patients have difficulty in tests of concept formation, problem solving, and rapid switching of cognitive set (Talland 1965, Butters & Cermak 1980), and recently they have been reported to have difficulty in certain tasks that require retrieval from semantic memory (Cermak et al 1978). Although the relationship between remote memory functions and other cognitive skills is far from clear, it seems reasonable that impairment involving retrieval from semantic memory or the deficient use of problem-solving strategies could affect remote memory and contribute to its impairment across all time periods.

Taken together, these considerations suggest that the extent of remote memory impairment in Korsakoff syndrome and its graded pattern reflect the operation of two factors:

1. Progressive anterograde amnesia, which exerts a greater effect on memory for events from recent years than events from remote years, and

which could explain the temporally graded pattern of remote memory impairment.

2. Cognitive deficits that affect in a uniform way the ability to reconstruct past memories, and which could explain the extensiveness of remote memory impairment.

Several lines of evidence indicate that the remote memory impairment, as observed in Korsakoff syndrome, is a distinct entity dissociable from and unrelated to anterograde amnesia. The patient H. M., for example, has profound anterograde amnesia for events that have occurred since his surgery in 1953, without measurable loss of remote memory from his premorbid period. In one study comparing H. M. and patients with Korsakoff syndrome on a remote memory test of famous faces (Marslen-Wilson & Teuber 1975), H. M.'s score for the 1950s and 1960s period was worse than that of patients with Korsakoff syndrome, but his score for the 1930s and 1940s was better. In another comparison involving case N. A., patients tested 1 to 2 hr after their fifth bilateral ECT, and patients with Korsakoff syndrome, all groups scored comparably on four tests of new learning capacity; yet the Korsakoff patients, and not the other patients, scored poorly on seven different tests of remote memory (Cohen & Squire 1981). Accordingly, the remote memory loss of Korsakoff syndrome is not inextricably coupled to anterograde amnesia.

This view of remote memory dysfunction as a distinct entity dissociable from anterograde amnesia in no way contradicts the common view that anterograde amnesia is closely related to brief, temporally limited retrograde amnesia. Indeed, a link between these two entities has been amply demonstrated in studies of experimental amnesia in animals (McGaugh & Herz 1972), and traumatic amnesia in man (Russell & Nathan 1946), and forms the basis of recent discussions of memory and brain function (e.g. Wicklegren 1979). More severe anterograde amnesia appears to be correlated with more prolonged retrograde amnesia. If the facts of retrograde amnesia are taken to imply a normal process whereby recently acquired memories gradually become resistant to disruption for a period up to a year or two after learning, then it is easy to imagine why a correlation between the severity of anterograde amnesia and the temporal extent of retrograde amnesia should be observed. Any brain injury that interfered with the consolidation and elaboration of memory would result in both a deficit in the formation of new, enduring memories (anterograde amnesia) and a deficit in recently acquired memories that were undergoing consolidation and elaboration when the injury occurred (brief retrograde amnesia).

Summary

The available data concerning retrograde amnesia and remote memory dysfunction now appear to resolve much of the confusion that has clouded these issues. Brief retrograde amnesia and extensive remote memory dysfunction appear to be distinct entities. Brief retrograde amnesia has been demonstrated most clearly in the amnesia associated with ECT, but it seems reasonable to suppose that it is present as well in case H. M. Extensive remote memory impairment has been clearly demonstrated in the Korsakoff syndrome. Remote memory dysfunction is presumably related to the involvement of brain regions in addition to those that are affected in more circumscribed amnesias (e.g. the medial temporal region for case H. M. and the dorsal thalamus for N. A.) and might be related to certain cognitive deficits superimposed on amnesia. Based on the available data, one might conjecture that for amnesias presumably caused by temporal lobe dysfunction, remote memory impairment implies damage in areas beyond the medial temporal region. The post-encephalitic patient who exhibits remote memory impairment (Albert et al 1980) in the context of temporal lobe and frontal lobe damage might be an example of this circumstance. For diencephalic amnesia, one might conjecture that severe remote memory loss implies damage in areas beyond the dorsal thalamus. The Korsakoff patient is presumably an example of this circumstance.

PRESERVATION OF LEARNING AND MEMORY IN AMNESIA

The fact that amnesic patients seem to perform well under some conditions has generated considerable interest because of the clear relevance of such findings to the nature of amnesia and the organization of normal memory.

Perceptual-Motor Skills

The best known examples of preserved learning and memory lie in the domain of perceptual-motor skills. Case H. M., for example, exhibited progressive learning of a mirror-tracing task across three days of testing, despite reporting on each day that he had no memory of having performed the task before (Milner 1962). Similarly, H. M. (Corkin 1968) as well as post-encephalitic patients (Brooks & Baddeley 1976) and patients with Korsakoff syndrome (Cermak et al 1973) were able to learn and remember over days, sometimes at a rate comparable to that of control subjects, the hand-eye coordination skills needed for a pursuit-rotor task. This task requires the tracking of a revolving target with a hand-held stylus. In the last few years, additional testing procedures have been cataloged, like those

involving fragmented drawings or certain kinds of cues, that also can elicit signs of retention in patients who are by other indications profoundly amnesic (Weiskrantz 1978).

There have been two general views of these matters. On the one hand, the finding that patients can sometimes demonstrate learning or retention behaviorally without reflecting it in their verbal reports has suggested that amnesic patients do not have access to their memories. By this view the ability to demonstrate certain kinds of learning and retention does not require this sort of access, and amnesia is fundamentally a retrieval deficit (Weiskrantz 1978). On the other hand, amnesia has been considered to reflect essentially a deficit in the formation of memory. This view recognizes that amnesic patients may perform well or even normally at certain tasks, but takes these data as a suggestion that different forms of memory are differently organized in the nervous system and that the amnesic syndrome affects some forms but not others. The brain regions damaged in amnesia, while necessary for many or most kinds of learning and memory, may not be required for certain other kinds. Consistent with this view is the recent work that has identified a domain of information processing that is spared in amnesia (Cohen & Squire 1980, Cohen 1981). This work also sheds light on the important observation that patients can demonstrate certain memory capabilities without having explicit access to their memory via verbal report (Weiskrantz 1978).

Declarative and Procedural Knowledge

Normal subjects can learn to read geometrically inverted or otherwise transformed text and can retain such pattern-analyzing skills for months (Kolers 1979). Amnesic patients (case N. A., patients with Korsakoff syndrome, and patients receiving ECT) and control subjects were asked to read sets of words that were reversed by a mirror. The amnesic patients improved their skill at this task at a normal rate over a period of three days and retained the skill at a normal level three months later. This occurred despite amnesia for aspects of the testing situation and despite profound amnesia for the specific words that had been read (Cohen & Squire 1980).

This finding suggests a distinction between information that is based on rules or procedures and information that is based on specific items or data. Thus, amnesic patients can learn the procedures needed for acquisition and retention of mirror-reading skills, but cannot remember the specific data, i.e. the words, that result from applying these procedures. Procedural learning, in contemporary psychology (Rumelhart 1981, Cohen 1981), is considered to result in modification or tuning of existing schemata (Bartlett 1932) (processes specialized for the interpretation of environmental events and for

operating in the world). In the case of mirror-reading, schemata involved in reading can apparently be modified in long-lasting ways.

This distinction was developed in the artificial intelligence literature (Winograd 1975) and is similar to previous distinctions concerning the representation of knowledge: knowing how and knowing that (Ryle 1949); habit memory and pure memory (Bergson 1910); memory without record and memory with record (Bruner 1969). The evidence now suggests that such a distinction is honored by the nervous system, and that these two domains of information depend on fundamentally different kinds of neurological organization. Although this distinction may not permit all tasks to be neatly dichotomized, it should be useful in predicting what is affected or spared in amnesia.

The possible usefulness of the declarative-procedural distinction to questions about the neurological organization of memory has recently been developed in some detail (Cohen 1981). Thus, the ability to develop and store declarative memory (all the bits of specific-item information that are the subject of conventional memory experiments like faces, words, and shapes) depends on the integrity of the particular bitemporal and diencephalic brain structures affected in amnesia. By contrast, motor skills and mirror-reading are taken as examples of procedural learning, which can occur in a normal way in the absence of these particular brain structures. Moreover, procedural knowledge is considered by its nature to be implicit —accessible only by engaging in or applying the procedures in which the knowledge is contained. Many skills, like playing golf or tennis, proceed despite poor access to "the specific instances that led to the perfection of the [skill]." These instances "change the rules by which [one] operates, but are virtually inaccessible in memory as specific encounters" (Bruner 1969, p. 254). The critical feature that is procedural here is that there can develop in memory a representation based on experience that changes the way an organism responds to the environment, without affording access to the specific instances that led to this change. Accordingly, procedural learning applies to more than just the acquisition of motor skills.

The neural systems specialized for interpreting and operating in the environment that subserve procedual learning may be phylogentically more primitive than those subserving declarative learning. The acquisition of declarative knowledge is dependent on specific structures in the bitemporal and diencephalic regions. Procedural learning appears to be independent of these brain structures and, since it is considered to involve changes in existing schemata, may be intrinsic to the neural systems in which it occurs. Habituation and sensitization, which can be demonstrated in invertebrates possessing relatively simple nervous systems (Kandel 1976), would appear to be examples of what has been termed procedural learning. Modification

of synaptic efficacy can occur in existing networks, resulting in a specific change in how the organism operates in the environment. However, memory for the specific instances that cumulated in this change, i.e. declarative knowledge, does not seem to be necessary in these cases.

Indeed, it is an intriguing possibility that the capacity for declarative learning emerged relatively late in evolution, perhaps as greater mobility and longer life spans made it important to maintain a (declarative) record of time and place information. Some forms of classical conditioning, as recently described in *Aplysia* (Walters et al 1979), might also reflect procedural learning. It is interesting that two amnesic patients (one post-encephalitic and one with Korsakoff syndrome) were able to acquire aversive (eye-blink) conditioning despite being unable, while still seated in front of the apparatus, to describe the learning experience or recount that they had received air puffs to the eye (Weiskrantz & Warrington 1979). Further work is needed to know if this or other forms of classical conditioning can in fact be acquired at a normal rate in amnesia and whether it should therefore be regarded as a preserved capacity.

Semantic vs Episodic Memory and Reference vs Working Memory

It is helpful to contrast the declarative-procedural distinction to two distinctions that have been advanced recently in the context of amnesia and brain function: *semantic* vs *episodic memory* (Kinsbourne & Wood 1975) and *reference* vs *working memory* (Olton et al 1979). It seems unlikely that the deficit in amnesic patients involves episodic autobiographical memory that has a specific time and place, but not semantic memory (context-free knowledge of facts, language, or concepts). Amnesic patients have seemingly equal difficulty acquiring both new episodic information (e.g. the events of a visit to Sacramento) and semantic information (e.g. the capital of California is Sacramento), and their retrograde amnesia applies to both spheres as well (Cohen & Squire 1981).

Likewise, the working memory-reference memory distinction developed from studies with experimental animals does not seem to fit the facts of human bitemporal amnesia. Reference memory, postulated to be spared in the case of hippocampal damage, is that aspect of a task that is constant from trial to trial. Working memory refers to aspects of a task that are useful for only one trial and not for subsequent trials. Thus, the constant features of a task are considered to be protected from the effects of hippocampal damage. In amnesia, however, simple repetition is not sufficient to insure learning (Drachman & Arbit 1966). Moreover, procedural learning is thought to be possible in amnesia because of the special nature of this information, not because such information is repeatedly available.

The notion of spatial maps and hippocampal function, developed also from study of experimental animals (O'Keefe & Nadel 1978), may have relevance to the ideas presented here. Whereas a literal version of this proposal does not fit well the findings from human amnesia (Squire 1979, Squire & Zola-Morgan 1982), a more abstract notion of spatial mapping might be made consistent with the idea that the brain regions damaged in amnesia are involved in establishing a specific kind of representation in memory.

Summary

The neuropsychological data, together with ideas founded in the cognitive sciences, suggest a distinction between procedural and declarative knowledge as a way of understanding what is spared and what is not spared in human amnesia. Procedural learning includes motor skills and certain cognitive skills and can proceed normally in amnesia. Declarative learning includes specific facts and data that are the subject of most contemporary memory studies and is impaired in amnesia.

ANATOMY OF AMNESIA

The preceding sections review neuropsychological aspects of diencephalic and bitemporal amnesia. It has also been of considerable interest to identify the specific brain structures which when damaged cause amnesia. Since this topic is the subject of several recent reviews (Brierley 1977, Horel 1978, Mair et al 1979, Squire 1980b), it is considered only briefly here. Most neuroanatomical discussions begin with the simplifying assumption that amnesia results when damage occurs to one of a group of functionally interrelated structures. In this sense the idea that damage in the hippocampal region (Scoville & Milner 1957) or in the mammillary bodies (Brierley 1977) can cause amnesia has been easy to accept because of their close anatomical relationship. Indeed, a functional link between hippocampus, fornix, and mammillary bodies was proposed decades ago (Papez 1937).

Yet the suggestion that diencephalic and bitemporal amnesia might be distinct entities raises the possibility that this functional link might not be so obligatory as was previously thought. Recent anatomical and neuropsychological data support this idea. In the rhesus monkey a substantial projection from the subiculum of the hippocampal formation is directed not only through the fornix but also to a variety of cortical and subcortical structures including amygdala, cingulate gyrus, entorhinal cortex, perirhinal cortex, and medial frontal cortex (Rosene & Van Hoesen 1977). Since the fornix projection to the mammillary bodies need not be viewed as the only significant output of the hippocampal formation, these structures need not be

viewed as a unitary anatomical system that either is or is not involved in amnesia. That is, as the connectivity between these regions is relaxed, it becomes easier to understand how lesions in the two regions could lead to different neuropsychological findings. In any case, it is well known that separate lesions in two brain regions, even if they are connected to some degree, produce markedly different patterns of brain disorganization and reorganization (Lynch 1976).

These neuroanatomical considerations notwithstanding, if both these regions were part of a unitary functional system, then damage to the fornix should also cause amnesia. However, in 50 cases that could be identified as having fornix damage, only three involved memory loss (Squire & Moore 1979). Though these data can often be faulted for lack of neuropathological confirmation or neuropsychological testing, it is worth mentioning that the best known case of bilateral fornix damage and memory loss (Sweet et al 1959) had a relatively mild amnesia (a difference between IQ and Wechsler Memory Quotient of only 13 points), compared to the amnesias described in virtually all contemporary studies. Fornix transection in the monkey has been reported to produce a memory deficit (Gaffan 1974), but also has been reported to be without effect on tasks sensitive to amnesia (Moss et al 1980). The discussion that follows accepts as a working hypothesis that diencephalic and bitemporal amnesia are distinct entities and considers what specific brain structures in each region have been linked to amnesia.

Diencephalic Amnesia

Our understanding of this topic comes largely from clinico-pathological studies of Korsakoff syndrome. Recent reviews (Brierley 1977, Mair et al 1979) agree that damage to the mammillary bodies correlates invariably with this syndrome, but uncertainty remains as to which lesions are correlated most strongly with the memory disorder itself. In their influential monograph on the Wernicke-Korsakoff syndrome, Victor et al (1971) identified five cases in their series where brain damage was apparently limited to the mammillary bodies and where memory loss was not observed. They suggested that the dorsomedial thalamic nucleus was the critical structure, since it was damaged in all 38 of their cases who exhibited amnesia. Since the mammillary bodies were also damaged in all these cases, their data are just as consistent with the hypothesis that lesions in both structures are required to cause amnesia.

Two thoroughly studied cases recently available for autopsy (Mair et al 1979) bear on these conclusions. Both these patients had bilateral lesions in the medial nuclei of the mammillary bodies and also a band of gliosis lying bilaterally between the third ventricle and the dorsomedial thalamic nucleus. Uncertainty about nomenclature, together with the indistinct

boundaries of the medial thalamic nuclei, were considered to complicate comparisons between these lesions and those described by others. Mair et al (1979) suggested that lesions in both regions might be needed to cause amnesia, or that lesions in mammillary bodies alone might be sufficient if they were large enough.

Unfortunately, the number of cases with adequate neuropsychological and pathological information is not sufficient to permit further resolution of these issues in a definitive way. In one series of 11 cases of Korsakoff syndrome for which neuropathological material was available, each patient was reported on the basis of clinical examination to have amnesia, and each had damage to the mammillary bodies. Thalamic nuclei were involved in some cases and not in others. The dorsomedial thalamic nucleus was damaged in only seven of the 11 cases (Brion & Mikol 1978). Whereas this report appears to favor the view that damage in the mammillary bodies is preeminent in diencephalic amnesia, at least in the case of Korsakoff syndrome, it also appears that damage limited to the region of the dorsomedial thalamic nucleus can be sufficient to cause amnesia. Memory loss, in association with vertical gaze apraxia and decreased alertness, has been reported in patients with infarctions affecting this region (Mills & Swanson 1978). Further, stereotaxic lesions of dorsomedial nucleus caused severe memory disturbances that were reported to subside within one year (Orchinik 1960). However, memory testing here depended on the Wechsler Memory Scale, which can be an insensitive measure of amnesia (Mair et al 1979), and no pathological information was provided. Finally, case N. A. has been shown by CAT scan to have damage in the left dorsal thalamus, in a region corresponding to the position of the dorsomedial nucleus (Squire & Moore 1979).

The available literature does not lead to easy conclusions about the relative roles of the mammillary bodies and dorsomedial nucleus in human amnesia. Perhaps lesions in either region can cause some degree of amnesia, and lesions in both regions cause more severe amnesia. In any case, the traditional view that damage to the fornix-mammillary system causes amnesia seems less secure than it once was, while damage to the dorsal thalamus seems able to cause amnesia.

The effects of dorsomedial nucleus or mammillary body lesions in experimental animals seem consistent in a general way with the findings in human patients, but many questions remain. Lesions of the mammillary bodies seems not to affect learning and memory in a global way (see Woody & Ervin 1966 and references therein), though the learning of an alternation task was impaired in rats (Rosenstock et al 1977). Dorsomedial nucleus lesions have been reported to affect memory in cats (Pectel et al 1955) and monkeys (Schulman 1964). These findings may need to be reevaluated in

the light of the demonstration that certain kinds of learning can proceed normally in human amnesia (Cohen & Squire 1980). That is, before concluding on the basis of negative evidence that a specific brain structure is not involved in learning and memory, it must be clear that the behavioral tasks used to assess memory are the kind at which human amnesics do not succeed.

Bitemporal Amnesia

Information about bitemporal amnesia comes largely from surgical cases in which portions of the temporal lobes have been removed bilaterally in an effort to relieve intractable epilepsy. As is now well known, the medial temporal region became clearly linked to memory after 1953 when it was discovered that bilateral resection of this region resulted in profound and lasting amnesia (Scoville & Milner 1957). The removals extended posteriorly along the medial surface of the temporal lobes for a distance of approximately 8 cm from the temporal poles and included uncus, amygdala, hippocampal gyrus, and the anterior two-thirds of the hippocampus. The noted case, H. M., was one of two patients to undergo this procedure. Severe amnesia was also observed in two other well-studied cases (P. B. and F. C.), who sustained left unilateral resections, and who had preexisting pathology of the right temporal lobe (Penfield & Milner 1958).

Several lines of evidence have suggested that damage to the hippocampal formation may be responsible for the amnesia in these cases. In five of six cases where bilateral resections extended posteriorly 4.5 to 6 cm so as to include uncus, amygdala, but only anterior hippocampus, the memory loss was not so severe as in case H. M. (Scoville & Milner 1957). [The remaining case, a paranoid schizophrenic (Case D. C.), was considered to have as severe amnesia as H. M. despite this limited removal.] In another case in the same series, where the resection was limited to the uncus and the amygdala, no amnesia resulted (Case I. S.). In addition, in the case of unilateral temporal lobe resections, which are associated with verbal or nonverbal (material-specific) memory deficits, the severity of the deficit was correlated with the extent of involvement of the hippocampal zone (Milner 1974). Finally, the notion that hippocampal damage is critical to the amnesic effects of medial temporal resections seems supported also by neuropsychological study of patients sustaining left or right amygdalotomy (Andersen 1978). These patients exhibited some behavioral deficits but were not amnesic and scored normally on tests of delayed recall.

The interpretation of these findings is complicated to some extent by the lack of a reported case of well-documented amnesia with bilateral damage limited to the hippocampus. All cases with hippocampal damage have damage to other structures; and this includes the surgical cases just re-

viewed as well as post-encephalitic cases, where lesions also occur in cingulate gyrus and frontal lobes (Hierons et al 1978), as well as cases of vascular disease, anoxia, and degenerative disease (see review by Horel 1978). Accordingly, although one could suppose from the surgical cases that hippocampus is the critical structure, the data are also consistent with the view that amnesia depends on conjoint damage to the hippocampus and the more anterior structures included in the resections, i.e. amygdala and uncus. Recently, these two hypotheses were tested with monkeys who had received separate or combined lateral damage to hippocampus and amygdala (Mishkin 1978). Only monkeys with the combined lesion were severely impaired on delayed nonmatching to sample, a test of the sort at which human amnesics fail. In this task, the monkey first displaces a single stimulus object to find food. Then, after a delay, in this case up to two minutes, the monkey is given a choice between a novel object and the original object. Food is hidden under the novel object. Whether the hippocampus and amygdala contribute in different ways to the ability to perform this task, and whether hippocampal damage alone might be sufficient to cause impairment on some tasks, is not yet clear.

Recently, traditional views of bitemporal amnesia were challenged with the suggestion that amnesia might depend not on damage to hippocampus but on damage to the albal stalk or temporal stem, a band of white matter lying above and in close proximity to the hippocampus (Horel 1978). Horel contended that the temporal stem was necessarily damaged in the anterior approach used in operating on case H. M. Moreover, because of the position of the temporal stem relative to the hippocampus, the more posteriorly a hippocampal lesion is extended, the greater the damage to the temporal stem. This interpretation of bitemporal amnesia has now been directly tested.

Monkeys with lesions of the temporal stem (TS) and monkeys with hippocampal-amygdala (HA) lesions were tested on a delayed nonmatching to sample task, involving delays up to 10 min, and also on a two-choice pattern discrimination (Zola-Morgan et al 1981). Although histological confirmation of these lesions is not yet available, the TS lesions were done under visual guidance. The intended lesion of the temporal stem included 10–15 mm of its anterior-posterior extent using the wall of the lateral ventricle as a visual guide. The HA lesions were done by a combined anterior and lateral approach, designed to avoid damage to the temporal stem. The results were that HA lesions severely disrupted the ability to retain information across a delay, whereas TS lesions had no effect. By contrast, TS lesions severely disrupted pattern discrimination learning, which is consistent with the effects of temporal neocortical lesions (Mishkin

1954, Mishkin & Pribram 1954), whereas HA lesions produced only a mild impairment. These results do not support the recent hypothesis that the temporal stem has a critical role in memory functions. Retarded acquisition of visual discrimination habits in monkeys with temporal stem lesions, together with their normal ability to retain information across a 10-minute delay, suggests that the temporal stem, perhaps by virtue of its connections with temporal neocortex (See Horel 1978, for review), contributes to the ability to process visual information.

The effects of medial temporal lesions in monkeys have often seemed difficult to reconcile with data from studies of human bitemporal amnesia (Weiskrantz & Warrington 1975, Iversen 1976). The demonstration of a domain of learning and memory that is spared in amnesia (Cohen & Squire 1980) may help to bring these two areas of research into agreement. Thus, those tasks in which monkeys with hippocampal-amygdala lesions are not impaired may be those kinds of tasks that are spared in human amnesia. Conversely, deficits do seem to appear in those tasks that involve declarative memory and that are sensitive to human amnesia (Squire & Zola-Morgan 1982).

Summary

In agreement with the neuropsychological findings, available anatomical data from patients with diencephalic or bitemporal amnesia suggest that these amnesias need not result from damage to a single functional system. In the case of diencephalic amnesia, the mammillary bodies and the dorsomedial thalamic nucleus have been implicated, but it is not yet clear which structure deserves the greater emphasis. In the case of bitemporal amnesia, the evidence suggests that the hippocampal formation plays a crucial role in memory functions; the possibility also needs to be considered that the hippocampal formation and amygdala may function conjointly in this regard. An alternative possibility that temporal stem damage is responsible for amnesia now seems quite unlikely.

PERSPECTIVE

Not long ago it was reasonable to think of amnesia as a unitary disorder reflecting damage to a specific, tightly connected neuroanatomical system. Accordingly, memory tended to be viewed rather monolithically as information that could be stored and retrieved so long as this system were intact. The neuropsychological and anatomical facts now tell a richer story in which amnesia may reflect either of two disorders corresponding to damage

in the diencephalic or the medial temporal regions; and in which memory normally depends on the separate contributions of both these regions. Of course, in considering the data from any area of inquiry, one always seeks to discover patterns of similarity and difference. Here certain differences have been emphasized between the disorders associated with diencephalic and medial temporal dysfunction with the thought that these differences may point the way to more detailed understanding of how the brain accomplishes memory storage. Appreciation of these differences, however, should not obscure the many similarities that can also be found among the amnesias; nor the fact that to infer the existence of two distinct entities from these similarities and differences is to some extent arbitrary.

The importance to memory of the diencephalic and bitemporal structures affected in amnesia is believed to lie in their role in the establishment of memory at the time of learning and in the consolidation or elaboration of memory for a time after learning so as to permit effective retrieval. It also seems clear that this role is narrower than it once appeared to be, in the sense that it applies to particular domains of learning and memory and not to all domains. Thus, motor skills and certain cognitive skills have been proposed to belong to a class of learning that is termed "procedural." This kind of learning is spared in amnesia and therefore is independent of the diencephalic and medial temporal structures that are affected in amnesia.

Our understanding of memory and its neural substrates is still rudimentary. Yet the experimental work suggests a framework for thinking about these matters that should prove useful in neuropsychological studies of memory as well as in cellular studies of simpler forms of behavioral plasticity. While technological advances in the neurosciences make feasible ever more detailed analysis of the nervous system and its parts, it is useful to remember that to know about the function of the nervous system entails understanding the behavior that it subserves. If these various levels of analysis can all be applied to the problem of behavioral plasticity, i.e. memory, then we can expect to achieve eventually a good understanding of how neural activity can give rise to behavior. And that is an exciting prospect.

ACKNOWLEDGMENTS

My work is supported by the Medical Research Service of the Veterans Administration and by NIMH Grant MH24600-08. I thank Drs. Lynn Nadel, Neal Cohen, and Stuart Zola-Morgan for numerous stimulating discussions of the ideas and data presented here; and Elizabeth Statzer for preparing the manuscript.

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