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THE NEUROPATHOLOGY OF AMNESIA

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Contents

1. Introduction

The basic question of modern neuroscience concerns the way in which the nervous system controls behavior, and there has been a debate on whether in principle the brain acts as a unit (the *Gestalt*-like or holistic view) or whether individual portions of it perform rather independently (mosaicist view) (e.g. John, 1972; Lashley, 1950; Markowitsch, 1984, 1985a,b; Smith, 1979, 1981; Thatcher and John, 1977; Zülch, 1976). Evidence from a number of sources has made it clear by now that neither view fits the data available (e.g. Finger and Stein, 1982; Goldstein, 1930; LeVere, 1975; Markowitsch *et al.*, 1985; Miller, 1984; Monakow, 1914; Penfield, 1975; Plum, 1975).

As a case in point, the state of activation in the mammalian nervous system, or in portions of it, varies from moment to moment and can be influenced at any time by a number of external and internal sources. It is furthermore influenced by the past experience of the subject, by genetic (pre-)dispositions and by age factors. Also, individual brain structures constantly interact so that changes in the activity of a particular neuronal assembly will influence the operation of a wide network of neurons (Irle and Markowitsch, 1983a, 1984a; Markowitsch, 1985a). Also, for different individuals, damage to similar brain loci may have rather different behavioral consequences (Markowitsch, 1984, 1985a,b). Together, these facts and further inter-individual differences in performance and brain structure (e.g. Buss, 1984; Gale and Edwards, 1983; Horowitz, 1969; Mayes, 1983; Merzenich *et al.*, 1975; Oscar-Berman *et al.*, 1984) preclude an exact determination of the functional consequences of a particular brain lesion.

Concerning the so-called higher intellectual functions such as learning and memory, there is a particularly high degree of plasticity in the mammalian brain as becomes evident from the diverse nature of results obtained from animals as subjects (e.g. Dru *et al.*, 1975; Lashley, 1929; Markowitsch *et al.*, 1985; Nakamura and Mishkin, 1980; Rosenzweig, 1984; Thompson, 1978), or with brain-damaged humans (e.g. Luria, 1980; Markowitsch, 1982a, 1984; Strub and Black, 1982; Teuber, 1974). Consequently, the view is not uncommon that "... to think of memories in terms of locality may be to search for a chimaera, for every memory must contain something that is the function of many (perhaps all) cortical areas—visual, auditory, motor, and sensory" (Fox, 1957, p. 919).

Nevertheless, in spite of the number of obstacles against attributing a precise relation between specific brain damage and its predictable consequences on behavior (recently reviewed by Damasio and Geschwind, 1985), there is a wealth of literature on one particular, long-lasting set of behavioral alterations which is said to follow certain kinds of circumscribed brain damage: the (global) amnesic syndrome(s).

Before describing this syndrome or set of syndromes, we will introduce some general terms necessary for understanding the symptomatology of memory disorders and then we will discuss possible subforms of mnemonic information processing.

2. Memory and its Disturbance

A general definition of memory is difficult, as the processing of information cannot be viewed as an isolated act, but has to be seen as dependent on perception, influenced by emotions and the imagination and embedded in the whole sequence from perception to action (Arnold, 1984; Fox, 1964). Sinz (1979, p. 19) defined memory in the following way (our translation) "With memory we mean the learning-dependent storage of ontogenetically acquired information, ... which at any time can be recalled, that is, can be made available for situation-dependent behavior". This is a plausible definition of memory, although cognitive psychologists have formulated a number of improvements and restrictions (e.g. Adams, 1967; Bruce, 1985; Neisser, 1982; Spear, 1978; Tulving, 1983). However, for the purpose of this article, the definition given above is appropriate, as is Spear's (1978) condensed definition saying that memory is "an organism's multidimensional representation of an episode (and not... a process)" (p. 45).

The representation of an episode requires that it be "perceived", "encoded", "stored" and that it can be "retrieved" (or otherwise may have been "forgotten"), to use the most common psychological expressions in this field. All these terms imply that the processing of information is time-dependent or time controlled. To what extent this is the case has been investigated with quite different approaches and with partly contradictory results. Pragmatically, the process of storage is usually divided into sequences of different duration which may be labeled "iconic memory", "short-term", "intermediate" and "long-term memory" (Atkinson and Shiffrin, 1968; Baddeley and Warrington, 1970; Gibbs and Ng, 1977; Milner, 1959; Neisser, 1970; Sperling, 1967; Squire, 1975) (Fig. 1).

This differentiation is generally oriented towards physiological–psychological mechanisms. The "iconic memory" or "echoic memory", lasting about a second or less, depends on the activation or deactivation of the receptors of a peripheral sense organ (Coltheart, 1983; Kolers, 1983; "short-term memory" is defined more variably, sometimes with reference to elements of cognitive psychology (remembering distinct items, the "magical number" 7 ± 2 of Miller (1956)), or with reference to neuropsychology or neurophysiology, covering then the span of time during which a (long-term) amnesic can remember information (Baddeley and Warrington, 1970; Cermak and O'Connor, 1933; Milner, 1959, 1966) or during which the potassium conductance of neurons is changed following learning (Gibbs and Ng, 1977) (Fig. 2). In "long-term memory", finally—in a vicious circle—only that information is represented which is stored beyond the time span of short-term memory. (Some authors divide long-term memory into a segment in which events are encoded for life and into another from which events can be recalled within the range of some months.) A neurophysiologically based model is given in Fig. 2.

With respect to long-term memory especially, the principal difficulty of experimental memory research becomes apparent, namely the fact that knowledge about stored information is basically gained only after that information has also become subject to

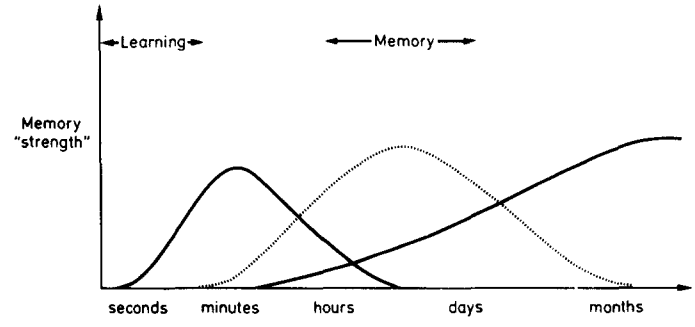

FIG. 1. Possible temporal relationships between different types of learning and memory. The duration and strength of short-term memory (left solid curve), long-term memory (right solid curve) and of an intermediate memory state (broken line) are illustrated. The temporal relationships shown would be in concordance with Hebb's (1949) model of a reverberatory circuit, dealing with short-term memory processing, and a slowly and gradually developing long-term memory trace, involving biochemical, structural changes. (The figure is based on Fig. 16-7 of Grossman (1977).)

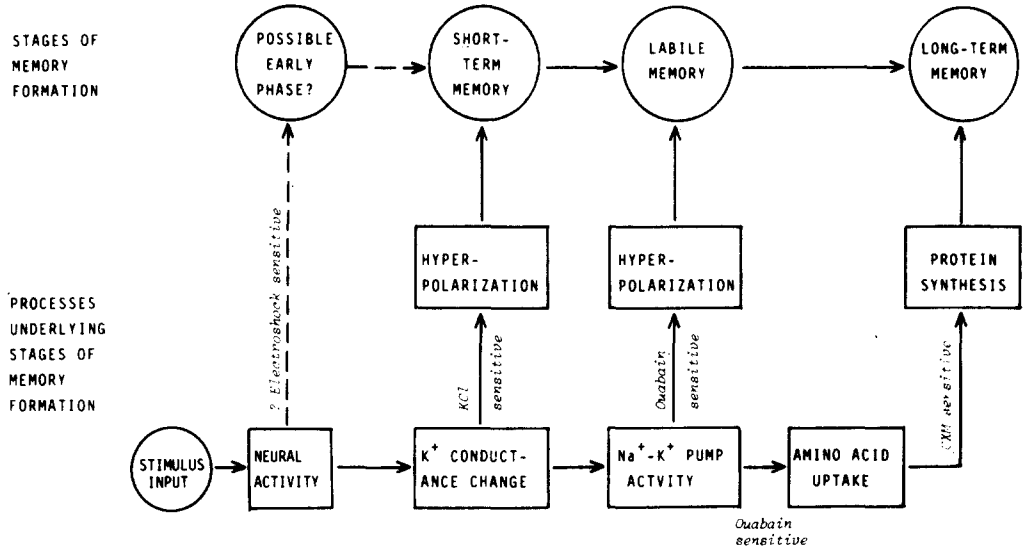

FIG. 2. Sequence of events in the formation of memory postulated by Gibbs and Ng (1977). (Reproduced from Fig. 17 of Gibbs and Ng (1977), with permission.)

retrieval. This reproduction of stored information may be reinforced with various retrieval aids ("forced-choice" paradigms, hypnosis, providing fragments as retrieval cues; e.g. Neisser, 1970; Warrington and Weiskrantz, 1968) (Fig. 3).

While the traces shown in Fig. 1 suggest the existence of more or less independent, sequential stores, several authors question whether memory can in reality be subdivided (e.g. Cermak, 1982; Craik, 1983; Haber, 1983; Johnson, 1983, 1985; Lewis, 1979; Meyer, 1984; Meyer and Meyer, 1982; Spear and Mueller, 1984), while others still defend this partitioning (e.g. Baddeley, 1982; Broadbent, 1983; Shallice, 1979).

Cermak (1982) summarized results from others which indicate that the three stores "iconic/echoic memory", "short-term memory" and "long-term memory" blur or melt into each other, with iconic/echoic memory lasting up to 25 sec (instead of only 1), and short-term memory extending over 20 items (instead of 7 ± 2). Long-term consolidation, Cermak reported, "could be disrupted anywhere from a few seconds (...) to a few days (...) to a few weeks (...)" (p. 48). Johnson (1983) assumed "that beyond the relatively short time it takes for chemical processes in the brain to respond to present external and internal events, memories do not further consolidate" (p. 99ff), and Meyer (1984) concluded that "structural traces are very stable entities, regardless of whether they have been in storage for seconds, minutes, hours, days, or years" (p. 83). The same position was also offered by Spear and Mueller (1984) who considered consolidation "an explicitly automatic process" (p. 113), that is, a process which continues independently of rehearsal or other proposed mechanisms.

On the other hand, Baddeley (1982) and Shallice (1979) argued for keeping the subdivisions of short- and long-term memory systems on neuropsychological evidence: the fact that cases exist which in essence manifest a normal performance on so-called long-term memory tasks, but which show extreme impairment in tasks requiring the short-term retention of verbal material (in so-called Brown–Peterson paradigms, e.g. three unrelated words or syllables have to be retained over an interval of less than 1 min with internal rehearsal being prevented by a counting task). Broadbent (1983), lastly, argued in favor of an even larger number of temporary, partly interacting memory forms, which can be differentiated from each other by aspects of encoding and by the properties of the material to be remembered.

While this discussion shows that psychologists do not agree on defining the manner(s) in which information is stored, it indicates that not all forms of material to be memorized will be encoded, stored and retrieved in similar ways. In fact, recent research emphasizes

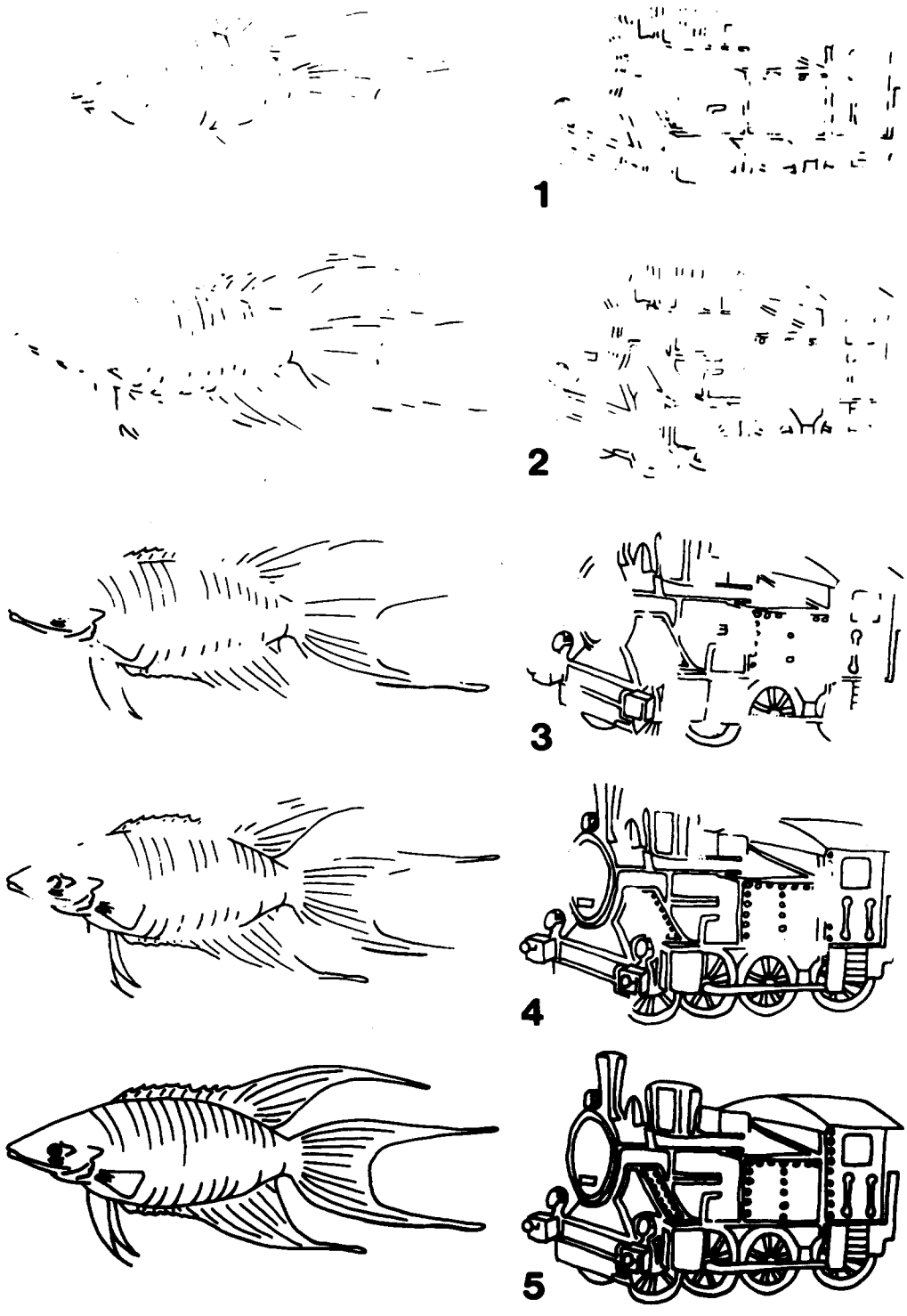

FIG. 3. Two examples of figures (a fish and an engine) corresponding to those in the Gollin's incomplete pictures test (Gollin, 1960), which are presented to subjects from version 1 (very incomplete) to version 5 (complete). It is assumed that the vague indications of an object in versions 1 and 2 do not usually allow an identification of the object, while they would do so if the complete object had been presented to the subject a short time before.

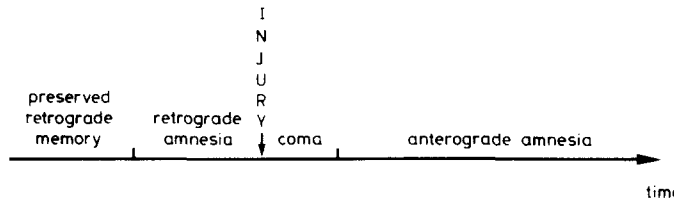

FIG. 4. Sequence of possible consequences of (traumatic) brain injury on memory. Modified from Fig. 4–1 of Levin *et al.* (1982) and Fig. 24.1 of Albert and Moss (1984).

differences in mnemonic processing which can be reflected in specific forms of brain damage.

2.1. FORMS OF MEMORY AND MEMORY FAILURES

Failure to retrieve information can either be related to the dimension of time or to the content (or material) of the event(s).

2.1.1. *Time*

A basic distinction relates to the failure to memorize events which happened after the occurrence of brain damage (*anterograde amnesia*) or beforehand (*retrograde amnesia*). Retrograde amnesia means that events which occurred and entered the memory before a certain period of time (e.g. traumatic brain injury) cannot be retrieved any more. In anterograde amnesia, events which the subject is confronted with after such a point of time cannot be memorized (Fig. 4).

While the period for which events cannot be memorized in anterograde amnesia may be indefinite (as is suggested from the case of a patient suffering from anterograde amnesia for more than 30 years up to now (Markowitsch (1985c)), that of retrograde amnesia is usually more limited (Fig. 5). A frequent and already old (Ribot, 1882) observation is that the period from which events are lost at first may go back a long time in the past but then, after the first days of the injury, may decrease gradually so that after some time only those events immediately preceding the time point of the injury may still be unavailable for recall.

A description of early concepts of anterograde and retrograde amnesia was provided by Levin *et al.* (1983).

2.1.2. *Material-specific memory failure*

Ribot (1882) also mentioned the existence of a hierarchical organization of memory with "automatic", "motor memory" or "habits" being less vulnerable to brain injury than other

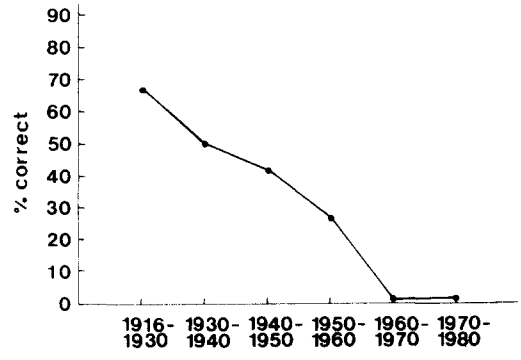

FIG. 5. Example for the frequent observation that retrograde amnesia is usually limited to and severest for the period immediately preceding the illness. Shown is the % of autobiographical information recalled from a patient (P.Z.), studied by Butters and Cermak, who at the age of 65 in 1982 developed an alcoholic Korsakoff syndrome. Three years prior to the illness he had published an autobiography from which the information could be taken for testing. (Adapted from Fig. 14 5 of Butters and Miliotis (1985).)

forms of memory. This distinction has recently been revived in a number of experimental and theoretical articles (e.g. Cohen, 1984; Martone *et al.*, 1984; Mishkin *et al.*, 1984; Mishkin and Petri, 1984), though it was already confirmed in a number of tests in the 1960s (e.g. Corkin, 1965, 1968; Milner *et al.*, 1968).

Apart from this distinction between "motor" vs "verbal" memory, a growing number of separable memory classes are becoming established both in human and nonhuman cognitive psychology. Among these distinctions are "working" vs "reference" memory (Honig, 1978; Olton *et al.*, 1979); "semantic" vs "episodic" memory (Tulving, 1972, 1985); "declarative" vs "procedural" memory (Winograd, 1975); "knowing how" vs "knowing that" (Cohen and Squire, 1980); "automatic" vs "effortful" encoding (Hasher and Zacks, 1979; Hirst and Volpe, 1984a) and "memory with record" vs "memory without record" (Bruner, 1969).

For the purpose of the present review—the relation of amnesic disorders to brain pathology—the individual dichotomies are still broad enough to show, at least theoretically, why certain forms of learning and memory are generally preserved in patients suffering from an amnesic syndrome. What these forms are in detail will be discussed below in relation to the specific case description given.

2.2. THE (GLOBAL) AMNESIC SYNDROME(S)

"The universality of amnesia is one of the striking characteristics of severe closed head injury" (Teasdale and Brooks, 1985, p. 189) but other causes of amnesic states have also been described (e.g. Whitty *et al.*, 1977). In most cases this amnesia is largely post-traumatic (Levin *et al.*, 1982) (Fig. 4) and covers usually but a short time period immediately following an insult (Russell, 1971; Teasdale and Brooks, 1985). In a few cases, however, a somewhat more distinct syndrome has been described, usually combining a short retrograde and an enduring anterograde (post-traumatic) amnesia: the global amnesic syndrome. The general features of this syndrome were recently given by Parkin (1984): (1) the pre-morbid levels of intellectual functions are maintained (except in cases with concomitant dementia), (2) short-term memory appears intact, (3) anterograde amnesia is severe and (4) a residual learning capacity exists, but is restricted to tasks not requiring access to the memory of specific personal events.

Although the general symptoms can, and frequently have been, viewed as one distinct syndrome (but see Lewis (1961) for an earlier, more conservative position), recent workers, including Parkin (1984), argue for the existence of more than one kind of amnesic syndrome (Rozin, 1976; Squire, 1982a; Squire and Cohen, 1984). This change in view is most likely due to the intense investigation of amnesic subjects during the last decade which has revealed that a number of specific areas of memory may deteriorate while at the same time others remain intact in amnesias of various pathology (Brooks and Baddeley, 1976; Cohen, 1984; Cohen and Squire, 1980; Huppert and Piercy, 1979; Markowitsch, 1985b,c).

3. Overview of the Pathology of Amnesia

Although the term "amnesic syndrome" seems to imply a rather circumscribed neuropathology, which is the case for the terms "aphasic syndrome" and "apraxic syndrome", a variety of different causes can be listed as possibly resulting in an amnesic syndrome (e.g. Benson, 1978) or in dementia (Benson, 1982; Joynt and Shoulson, 1985). (Occasionally, we will include in this section evidence from cases with dementia rather than amnesia. Although dementia is characterized by further symptoms of intellectual dysfunction, it usually includes amnesia, and Wells (1978), who gave a definition of the term, emphasized that memory loss is usually the earliest and most persistent symptom of dementia; cf. also Mayeux and Rosen (1983) and Pearce (1984a).) The most obvious relations exist between amnesia and vascular, degenerative or tumorous processes or other changes within the tissue of the nervous system.

3.1. VASCULAR SYSTEM

Occlusion or rupture of major arteries (Duvernoy *et al.*, 1981; cf. especially their Fig. 1) disturbs or prevents the normal metabolism within certain brain regions and may thereby lead to widespread and enduring amnesic states (Hurtig and Reivich, 1977; Reivich, 1977a,b). This has been found (or suggested) for all major arterial systems, such as the anterior cerebral or anterior communicating arteries (Alexander and Freedman, 1984; Damasio *et al.*, 1985b; Gade, 1982); the posterior cerebral artery (Langworthy and Fox, 1937; Ross, 1980a; Wilson, 1982); the middle cerebral artery (Mesulam *et al.*, 1976); the basilar artery (Hegglin, 1953; Labauge *et al.*, 1981) and the paramedian thalamic arteries (Casteigne *et al.*, 1980; Graff-Radford *et al.*, 1985; Guberman and Stuss, 1983; Schuster, 1936a,b, 1937a,b; Winocur *et al.*, 1984). Furthermore, transient global amnesia may be caused by vasospasms or other temporary constrictions within the brain's arterial system (Markowitsch, 1983). As with enduring amnesia, cases of transient global amnesia with angiographical records are available for each of the major arterial systems (cf. paragraph *Arteries* on p. 37 in Markowitsch (1983)).

3.2. DEGENERATIVE PROCESSES

Relationships between degenerative processes and dementia were already described quite early in this century (e.g. Alzheimer, 1907; Bechterew, 1900; Bolton, 1903; Pick, 1901, 1906). Alzheimer patients (Braunmühl, 1957; Katzman *et al.*, 1978; Reisberg, 1984) form the largest group of cases with amnesic defects and degenerative changes in the central nervous system, and although cortical atrophy was originally regarded as the main anatomical basis of this disease (Alzheimer, 1911; Braunmühl, 1957; Grünthal, 1930), more recently, changes in cholinergic systems of the basal forebrain (and partly of the brainstem) have been correlated with Alzheimer's disease (Arendt *et al.*, 1985; Bondareff *et al.*, 1982; Coyle *et al.*, 1983; Mann *et al.*, 1984; McGeer *et al.*, 1984), as well as the involvement of limbic system structures such as the hippocampal formation (Hyman *et al.*, 1984).

Other diseases which lead to cortical atrophy include Pick's disease (Braunmühl, 1930; Brun and Gustafson, 1978; Malamud and Boyd, 1940), Pick's and Alzheimer's disease in combination (Smith and Lantos, 1983), Creutzfeldt–Jacob disease (Brun and Gustafson, 1978; Roos and Johnson, 1978; Terry, 1976), Huntington's chorea (Brandt *et al.*, 1984; Terry, 1976; Tomlinson, 1978), Down's syndrome (Miniszek, 1983; Sinex and Merril, 1982) and various forms of viral encephalitis (Haase, 1978; Spatz, 1934; Tomlinson, 1978), including the acquired immune deficiency syndrome (AIDS; Shaw *et al.*, 1985), multi-infarct dementia (Sourander and Wålinder, 1977), as well as some rare diseases with unknown origin or of a "nonspecific" nature (e.g. Kim *et al.*, 1981), or with genetic bases (e.g. Rothner *et al.*, 1976).

Apart from cases in which the underlying atrophy takes place principally in cortical areas, there are morphological changes leading to amnesic disorders which can involve almost any other part of the brain, including noncortical telencephalic areas (e.g. Cummings and Benson, 1984; Kaiya *et al.*, 1974; Martone *et al.*, 1984; Mayeux *et al.*, 1983; Oscar-Berman *et al.*, 1973; Pirozzolo *et al.*, 1982). In those cases, however, in which the basal ganglia are primarily involved, the amnesic syndrome is only occasionally manifest. Benson (1983) in fact went so far as to reserve the term amnesia only for cases with cortical damage and the term forgetfulness for those with subcortical damage (cf. also Mayeux *et al.*, 1983 and Benson, 1984).

Degenerative changes as a consequence of epileptic attacks are frequently found in limbic structures such as the amygdaloid region and the hippocampal formation (Dam, 1982; Delgado-Escueta *et al.*, 1983; Goldensohn, 1977; Meldrum, 1975; Sarter and Markowitsch, 1985a; Scheibel *et al.*, 1974; Scholz, 1951; Veith, 1970). However, there are also a number of cases in which limbic structures degenerated independently of the existence of an epileptic focus (Glees and Griffith, 1952; Grünthal, 1947; Hierons *et al.*, 1978). This is most frequently true in Korsakoff's psychosis (Butters, 1984; Cutting, 1985; Victor *et al.*, 1971), in which the mamillary bodies and midline regions of the thalamus,

in particular the region of the mediodorsal nucleus, are affected (Gamper, 1928; Gudden, 1896; Kant, 1932; Markowitsch, 1982a; Remy, 1942; Tsiminakis, 1931), but is also found in cases which have other kinds of etiology, or even unknown causes (e.g. Kaiya *et al.*, 1974; Katz *et al.*, 1984; Kosaka *et al.*, 1977; Martin *et al.*, 1983; Oda, 1976; Schulman, 1957).

In animals it was recently found that the interruption of the mamillothalamic tract prevents seizures (Mirski and Ferrendelli, 1984). This surprising result suggests a role of the mamillary bodies and their main efferent connections in the propagation and perhaps initiation of generalized seizures.

3.3. TUMOROUS PROCESSES

Although patients with brain tumors (Zülch, 1965) in general have a poor prognosis (Bigner, 1977; Dubois, 1984), several striking cases have been given in the literature which manifested reinstatement of mnemonic functions following removal of the tumorous tissue, which is especially the case when the tumor originated from the periphery of the central nervous system and thus constituted a cyst (Cairns and Mosberg, 1951; Foerster and Gagel, 1934; Lobosky *et al.*, 1984). (For a classification of brain tumors see Dubois (1984) and Young (1983)).

Severe memory disturbances are usually found in cases with midline gliomas (Langfitt, 1977a) or with tumors infiltrating the third ventricle from the basis of the brain (Assal *et al.*, 1976; Beal *et al.*, 1981; Benedek and Juba, 1940, 1941; Burkle and Lipowski, 1978; Geffen *et al.*, 1980; Lechi *et al.*, 1975; Mehraein and Rothemund, 1976; Rodriguez and Lawson, 1982; Sachs *et al.*, 1962). Whitty *et al.* (1977) pointed out that the frequent observations of memory disturbances in these cases are most likely related to the large number of bilateral structures that are all situated close to each other in this region so that both sides of the hemisphere are likely to be affected.

Apart from the mamillary bodies and other hypothalamic regions the mediodorsal and anterior thalamic nuclei are frequently affected by the tumor (e.g. McKissock and Paine, 1958), but memory-related regions of the basal forebrain (cf., e.g. Damasio *et al.*, 1985b) and the fornix may also be affected (Cameron and Archibald, 1981; Zeman and King, 1958).

Only a few cases have been described with tumors in the temporal lobe that had any loss in memory functions, and this loss was then insignificant (or described as insignificant) (Cavanagh, 1958; Karvounis *et al.*, 1970).

3.4. OTHER POSSIBLE CAUSES OF AMNESIA

Apart from these primarily vascular, degenerative and tumorous changes in the nervous system, which make up the greater part of the cases with memory deficits, there are some further events with possible mnemonic complications.

3.4.1. *Traumatic lesions*

Traumatic lesions are the most prominent of these events and memory disturbances are their most frequently reported consequences (Clifton, 1983; Levin *et al.*, 1982; Rehwald, 1956; Thompson and Green, 1979). Thus, several reviews on traumatic amnesia are available (Alexander, 1982; Russell, 1971; Russell and Nathan, 1946; Teasdale and Brooks, 1985; Whitty and Zangwill, 1977; Williams, 1969).

Compared to the aforementioned causes of amnesia, traumatic amnesia more usually involves retrograde amnesia (e.g. Critchley, 1957; Fisher, 1966; Russell, 1935; Yarnell and Lynch, 1970) and, because head trauma can have such diverse causes, rather different cortical and subcortical regions have been described in the literature as related to mnestic disturbances when damaged. In a number of cases, head injuries may cause symptoms which parallel those of the Korsakoff syndrome (Czechmanek, 1954; Jarho, 1973). In

others with circumscribed injury, the mnemonic disturbance may be rather isolated as in case 1 of Ross (1980b), which only showed a unilateral loss of tactile recent memory. The most well-known case with a circumscribed traumatic brain injury and resultant persistent anterograde memory impairment is the patient N.A., first described by Teuber (Teuber, 1968; Teuber *et al.*, 1968) and subsequently investigated in greater detail by Squire and co-workers (Cohen and Squire, 1980, 1981; Squire and Moore, 1979; Squire and Slater, 1978; Squire and Cohen, 1982).

3.4.2. *Electroconvulsive therapy*

Another cause of amnesic states may be electroconvulsive therapy (ECT) which, according to Fisher (1985), 16% of American psychiatrists use and regard as the most effective way of treating chronic depression. The question as to whether ECT may cause brain damage was recently discussed extensively in a publication by Weiner (1984) and in the comments accompanying the article. ECT does have effects on both remote and recent memory when subjects are tested 40–80 min after their fifth treatment with ECT (Squire, 1974). However, when assessing the memory functions of former ECT patients six to nine months after therapy, Squire and Chace (1975) failed to obtain evidence for persisting memory impairment. Nevertheless, Squire recently came to the conclusion that "there is no question but that there is permanent loss" of memory following ECT (cited in Fisher (1985), p. 18; cf. also Squire (1984)).

3.4.3. *Brain surgery*

Brain surgery (such as stereotaxic brain operations or cortical resections) may in some cases lead to persistent amnesias (e.g. Scoville and Milner, 1957; Penfield and Milner, 1958), or to modality-specific memory deficits (Rausch *et al.*, 1977), while in others the impairment may be selective and/or transient (e.g. Novelly *et al.*, 1984; Wieser and Yasargil, 1982; Wycis, 1972), or an improvement of mnemonic functions may even be noted (Novelly *et al.*, 1984; cf. also Markowitsch, 1984). However, the interpretation of the data on surgically induced brain damage is of course rather difficult in light of the fact that some personality aspects and brain activity in these patients are usually abnormal before surgery.

3.4.4. *Infections*

As to the viral infections of the central nervous system, a number of case reports on herpes simplex encephalitis (Miller and Harter, 1977; Spatz, 1934; Thompson and Green, 1974) have found specific mechanisms of deficient long-term information processing in the patients (Adams and Miller, 1973; Barbizet *et al.*, 1978; Cermak and O'Connor, 1983; Damasio and Van Hoesen, 1985; Greenwood *et al.*, 1983; Klapper *et al.*, 1984; Mattis *et al.*, 1978; Starr and Phillips, 1970). A self-report on visual hallucinations during encephalitis was given by Mize (1980).

Sarcoidosis, another illness which might be caused by a viral infection or by tuberculosis (Esselier *et al.*, 1951; Matthews, 1965; Silberberg, 1977; Zeman, 1958), has also been observed to result in brain damage and in amnesia (Delaney, 1977; Hier *et al.*, 1983; Mehraein and Jamada, 1967; Sarter and Markowitsch, 1985a).

3.4.5. *Metabolic deficiencies*

Furthermore, amnesia has been related to hypoglycemia (Nichelli *et al.*, 1982; Schrappe, 1963), to various intoxications and drugs (Appel, 1977; Benson, 1982; Ely, 1922; Haase, 1978; Környey, 1931; Marcovitz and Alpers, 1935; Mashaly *et al.*, 1983; Oda, 1976; Pentschew, 1958a; Whitty *et al.*, 1977), to nutritional deficiencies (Busse, 1967; Pentschew, 1958b; Victor *et al.*, 1971; Victor and Silby, 1977) and to hypoxia and ischemia (Carney

and Anderson, 1981; Fahn *et al.*, 1979; Hirst and Volpe, 1984b; Langfitt, 1977b; Plum, 1973; Redington *et al.*, 1984; Volpe and Hirst, 1983a).

3.4.6. *Psychogenic loss of memory*

To complete this survey, psychogenic loss of memory (also named hysterical or motivated amnesia) should also be mentioned (Lewis, 1961; Lishman, 1971; Pratt, 1966; Stengel, 1966; Symonds, 1966). This mental alteration is characterized by a failure to have registered events shortly before and during emotional disturbance. It can be differentiated from other forms of amnesia by the typical loss of the ability to identify oneself by name (Croft *et al.*, 1973; Fisher and Adams, 1964; Lishman, 1971; Pratt, 1966; Wilson *et al.*, 1950). Furthermore, the patients are usually younger than those with organic amnesia (Fisher and Adams, 1964), they suffer their attacks frequently while being alone or away from home, appear indifferent in mood with respect to their memory loss, and their condition can usually be traced back to inopportune events (Balastrieri *et al.*, 1974; Croft *et al.*, 1973; Fisher and Adams, 1964; Wilson *et al.*, 1950). Other criteria for distinguishing psychogenic amnesia from other forms are the intact anterograde memory span in psychogenic amnesics, the rather variable span of the amnesic period and the frequent pre-amnestic personality disorders (Fisher and Adams, 1964; Patten, 1971; Steinmetz and Vroom, 1972).

4. Brain Lesions and Amnesia

Under this heading we will give a more detailed description of a number of cases in which amnesia was the result of circumscribed brain damage, with emphasis not on general neuropathological causes, but rather on the specific brain areas which were affected.

4.1. MEDIAL TEMPORAL LOBE DAMAGE

4.1.1. *General remarks on anatomy and functions of the temporal lobe*

The region of the medial temporal lobe is known as particularly vulnerable and, if damaged, as frequently resulting in mnestic alterations. Damage here is common in cases with epilepsy, Alzheimer's disease, senile dementia or Pick's disease (e.g. Ball, 1979; Corsellis, 1970; Gloor *et al.*, 1982; Sommer, 1980; Uchimura, 1928). Uchimura's description of 10 cases with selective degeneration in the Ammon's horn (as can be seen in 17 photographs showing damaged hippocampal tissue) and the article of Sommer (1980) provide impressive early examples of the particular vulnerability of the hippocampus towards various influences from the environment or from neuronal activity.

Apart from those cases in which only the medial temporal lobe area is affected and in which disturbance of memory is the prominent syndrome, there are other cases which usually involve more extensive damage, including the whole amygdaloid region, and the resultant symptoms have been called the Klüver–Bucy syndrome (Aichner, 1984; Dahlmann and Schaefer, 1979; Gascon and Gilles, 1973; Lilly *et al.*, 1983; Marlowe *et al.*, 1975; Shraberg and Weisberg, 1978; Terzian and Dalle Ore, 1955). First described for monkeys (Klüver, 1958; Klüver and Bucy, 1937), it is characterized by visual agnosia, an increased oral activity (that is, a tendency to examine all objects orally), hypermetamorphosis (tendency to take notice of and attend to every visual stimulus), hypersexuality, placidity (diminution or complete absence of emotional responses), changes in dietary habits and memory disorders. According to Aichner (1984), who investigated 53 cases with a Klüver–Bucy syndrome, hyperorality was observed most frequently (in 98% of the cases), followed by hypersexuality (79%), hypermetamorphosis (77%), amnesia (77%), placidity (74%), visual agnosia (42%) and bulimia (28%).

The syndrome may appear in cases with rather divergent brain damage and may follow a quite divergent time course as well (Aichner, 1984). Poeck (1985a) summarized clinical

and clinicoanatomical observations in two tables and stated that (1) "bilateral lesions of Ammon's horn are a sine qua non for the production of the syndrome" (p. 260) and (2) "the precise localization of the components has so far not been possible" (p. 260).

A widely discussed and still unresolved question is whether particular loci exist within the medial temporal lobe whose damage most probably causes amnesia. The areas under consideration include the hippocampus proper or the hippocampal formation (Bechterew, 1900; Milner, 1974; Penfield and Mathieson, 1974; Scoville and Miller, 1957; Woods *et al.*, 1982; Zola-Morgan *et al.*, 1985); the hippocampus together with the amygdala (Mishkin, 1978; Zola-Morgan *et al.*, 1983a); the temporal stem, that is, the white matter that contains afferent and efferent connections of the temporal cortex and the amygdala, but not of the hippocampus (Horel, 1978); fiber systems connecting the hippocampus with other brain regions (Van Hoesen *et al.*, 1985); the entorhinal cortex (Moss *et al.*, 1981); neocortical portions of the temporal lobe (Horel and Pytko, 1982; Horel *et al.*, 1984; Penfield, 1975; Penfield and Perot, 1963) and combined damage of medial and lateral regions of the temporal lobe (Gonser, 1983).

Although the issue is not yet resolved as to just what each of these systems contributes to long-term information processing, comparing the facts on which each particular hypothesis has been based makes it likely that part of the discrepancies in interpretation can be attributed to differences in testing conditions (e.g. to the tasks selected) while others may be due to a massed lesion or to an added lesion effect (e.g. combined damage of amygdala and hippocampus vs single damage of the two structures or of the fiber systems of the temporal stem only). For instance, as has been shown in recent reviews and experimental data for the amygdala (e.g. Murray and Mishkin, 1985; Sarter and Markowitsch, 1985a,b), this structure is involved to a higher degree in mnestic information processing than had been previously assumed (Orbach *et al.*, 1960; Scoville and Milner, 1957). Furthermore, it should be mentioned here that several authors prefer to speak of memory *circuits* in which structures such as the amygdala or the hippocampus are embedded, each being one of several key stations (cf., e.g. Markowitsch, 1985a; Mishkin, 1982).

In connection with this last point we would like to stress, as have others before (e.g. Bear, 1979; Williams, 1969; Poeck, 1985b), that the temporal lobe has a particularly high degree of inter-connections and is a morphologically as well as a functionally diverse brain region. Within the posterior half of the temporal lobe we have sensory and sensory association cortex, especially for the visual, auditory and olfactory modalities (cf., e.g. Gross, 1973; Jones and Powell, 1970; Markowitsch *et al.*, 1985; Mishkin, 1982; Seltzer and Pandya, 1978), and within its medial half we have the highly structured regions of the hippocampal formation and the amygdaloid complex (cf. Stephan, 1975). As has been proposed since Broca (1878) and Papez (1937), the medial temporal lobe regions and their associated fiber systems form part of the limbic lobe which constitutes a kind of buffer region between phylogenetically recent and phylogenetically old brain structures (MacLean, 1954). Papez proposed the existence of a circuit interconnecting several of these structures in an aligned, chain-like way and involved in the processing of emotional information. Later this circuit was regarded as relevant for mnestic information processing (e.g. Kornhuber, 1973) and recent neuroanatomical evidence (Fig. 6) shows in fact that those regions most intensely inter-connected are also most closely related to long-term memory (Irle and Markowitsch, 1982a,b; Rosene and Van Hoesen, 1977).

As Fig. 6 shows, one of the temporal lobe structures, the "subicular cortex" (part of the hippocampal formation), is closely connected to those two diencephalic structures which are most frequently mentioned as resulting in amnesia after being damaged (Fig. 7) (cf., e.g. Mair *et al.*, 1979; Markowitsch, 1982a). However, emphasizing particular structures to the neglect of others is of doubtful usefulness, as can be seen from Figs 6 and 7 as well as by considering the multiple connections of the limbic system structures (e.g. Nauta, 1958, 1972, 1979), and this has led to the rejection of the traditional concept of the limbic system (e.g. Goldberg, 1984; Swanson, 1983).

With these remarks in mind, we will now describe the available evidence on humans with

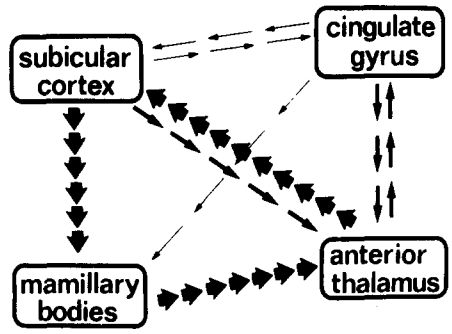

FIG. 6. Schematic illustration of the inter-relations between regions of the Papez circuit as traced in the study of Irle and Markowitsch (1982a). Arrows denote the direction of projecting fibers, the thickness of the arrows corresponds to the magnitude of the projection, as inferred from the number of retrogradely labeled cells. The most intense projection (more than 90% of the labeled cells) bypasses the cingulate gyrus and directly inter-connects the anterior thalamus and the subicular cortex. (Reproduced from Fig. 12 of Irle and Markowitsch (1982a), with permission.)

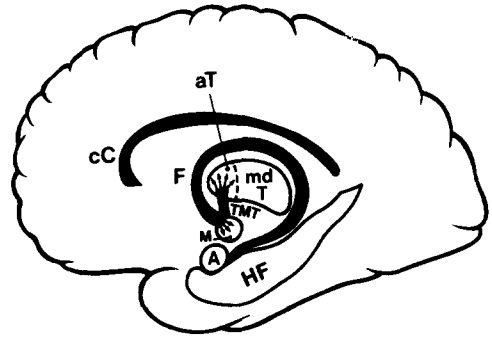

FIG. 7. Schematic sagittal section through the human brain, indicating the approximate position of the corpus callosum (cC) and structures most frequently implicated in memory. Abbreviations: A, amygdala; aT, anterior thalamus; F, fornix; HF, hippocampal formation; m, mamillary bodies; mdT, thalamic mediodorsal nucleus; TMT, tractus mamillo–thalamicus.

restricted, usually bilateral, temporal lobe damage and amnesia, starting with the most widely known and most intensely studied case: H.M.

4.1.2. *Case H.M.*

In September 1953 W. B. Scoville performed a bilateral resection of medial temporal lobe regions in a young male, whose name is abbreviated as H.M., in order to treat his otherwise intractable epileptic seizures. According to Scoville, the resection performed on H.M. included "portions of the hippocampus and hippocampal gyrus bilaterally" as well as "the uncus and amygdala" (Scoville and Milner, 1957, p. 20). Figure 8 gives a somewhat simplified picture of the position of the hippocampal formation and the amygdala in the human brain. Based on the operations on other patients which included hippocampal and amygdaloid portions to different degrees, Scoville and Milner (1957) later concluded that removal of the hippocampus but not the amygdala was critical for producing the global amnesic syndrome which followed the surgery. While they originally considered the operation on H.M. as "frankly experimental" (p. 11), they nevertheless held it to be justified since the patient had been unable to work pre-operatively and because treatment by nonsurgical methods had failed to improve his status. (In 1968, Scoville no longer considered such an operation as justified because of the probability of inducing an enduring amnesic state, he criticized neurosurgeons who had reported in 1967 that they still performed this kind of surgery.)

The extent of neuronal tissue removal was particularly large in H.M., as electro-

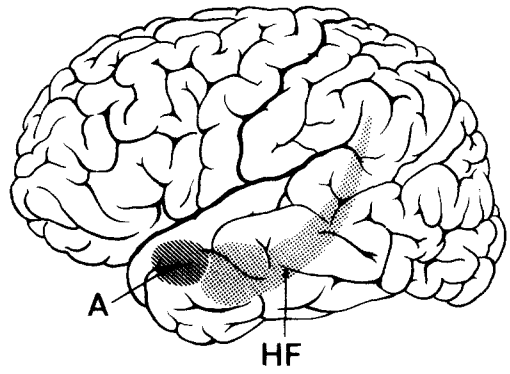

FIG. 8. Lateral view of the human brain indicating the approximate position and extent of the hippocampal formation (HF) and the amygdala (A) within the *medial* temporal lobe.

physiological recordings had failed to reveal a critical epileptic focus either in the right or left temporal lobe of H.M.

During the days following surgery, H.M. was unable to identify the hospital staff or to find his way to the bathroom; he also seemed incapable of orienting himself within the hospital. Furthermore, his pre-operative (remote) memory seemed to be impaired. He no longer knew that his favorite uncle had died three years previously, nor that he had been brought into a hospital (though he could remember a few events which happened immediately before his admission). He remembered earlier events vividly and apparently without any mistakes.

After the operation he still had occasional epileptic attacks but they were much less frequent or severe than previous ones (Scoville, 1968; Scoville and Milner, 1957). As Scoville wrote in 1968, H.M. had no sexual outlets following surgery and apparently also had no need of them. His social behavior appeared normal apart from the fact that he frequently excused himself for having forgotten the names of persons he had been introduced to (Scoville, 1968). He dressed himself adequately though he had to be reminded to shave. His vocabulary was above average and he understood the point of a joke, even when it involved semantic ambiguity (Milner *et al.*, 1968).

H.M. is the "classical" patient with an amnesic syndrome, being highly incapable of memorizing information long-term which he has been confronted with since the operation, otherwise he has above average intelligence and an intact personality. In the following we will give a description of his general behavior and some of his difficulties in performance during certain periods after the operation.

4.1.2.1. *The first years after surgery*

In their first extensive report on H.M., Scoville and Milner (1957) already noted that H.M.'s memory disturbances had not improved since 1953. For illustration they provided both anecdotal evidence and the results of formal neuropsychological tests. Even 10 months after his family moved into a new flat, H.M. still failed to find his way home, although he knew the address of his old home in which he had lived prior to the operation; he was unable to find the lawn mower, even when he had used it only the day before (Scoville and Milner, 1957). He did not recognize neighbors who had been visiting the family for the last six years (from 1957 onwards) (Milner, 1966). He would do the same jigsaw puzzle over and over again without any practice effect and would reread the same magazines day after day. Half an hour after having eaten lunch he did not remember the meal (Scoville and Milner, 1957), and he could not be left alone at home because he would allow strangers to enter, assuming that they were friends of the family whom he could not remember (Milner, 1966). (In the light of the recent distinctions between "habit", "skill", "motor" or "procedural" memory on the one hand, and "episodic memory" or "knowing that" on the other hand (see Section 2.1.1), the failure of H.M. to improve in solving the jigsaw puzzle is unexpected.)

H.M.'s first formal post-surgical psychological tests were performed one and a half years

after his operation, at the end of April 1955. Asked about the date and his age, he said he was 27 (instead of 29) and gave March 1953 as the date. He seemed to have little remembrance of his operation. His intelligence quotient, originally 104, increased post-operatively to 112 in 1955 (Scoville and Milner, 1957) and even to 117 in 1962 (Milner, 1962), but his memory quotient remained considerably below that of normals so that the difference between general IQ and memory quotient was striking. Other abilities such as abstract reasoning and sensory performance were not impaired (at least not as far as investigated until 1970). For the period which his retrograde amnesia covered, Scoville and Milner (1957) and Milner (1959) gave several years prior to his operation. Later, this period decreased to about one year (Milner, 1966). As H.M. acquired nearly no new information, he seemed to remember the old all the more vividly and took pleasure in repeating it. For instance, he enjoyed telling long anecdotes from his stay at school, his holiday experiences, the first epileptic attack and smoking his first cigarette (Milner, 1959, 1966).

In line with the distinction between "knowing how" and "knowing that", mentioned in Section 2.1, H.M. had considerable difficulties with "knowing that" something was the case, while being able to deal with the first form of information processing. Corkin (1968) showed that H.M.'s performance improved in tasks requiring rather stereotyped motoric abilities, such as keeping a stylus on a point of a rotating disc, bimanual tracking or tapping as quickly as possible on each sector of a divided circle. This means that H.M. remembered important behavioral sequences over days.

Furthermore, training did improve his performance in simple visual and tactile mazes, in which the time sequences for the required turns was so small that it lay within his short-term memory span, while the acquisition of more complex (that is, longer) mazes still remained impossible (Corkin, 1965; Milner, 1965) (Fig. 9).

The behavior of H.M. is frequently called upon as an example for the distinction between short- and long-term memory, and this aspect was especially investigated by Sidman *et al.* (1968) and Wickelgren (1968). While H.M. was able to reidentify without difficulty a word which he had seen 40 sec before, out of a series of nine words presented simultaneously (longer time spans were not tested), he had difficulties with nonverbal material (ellipses) after only 24 to 32 sec, which was explained by the investigators as a failure to memorize this material verbally (Sidman *et al.*, 1968).

As another case in point, H.M. was admitted to a Boston clinic in 1966 and 1967 for a series of tests. After having been checked in, he rang for the night nurse and asked where he was and why he had been hospitalized, which was apparently embarrasing for him. (He recognized that he was in a hospital from the surroundings.) It was also at this time that he made the poignant statement: "Every day is alone, whatever enjoyment I've had, and whatever sorrow I've had" (Milner *et al.*, 1968, p. 217).

When his father died in December 1967 he appeared irritable and intractable; one evening he disappeared from home in anger. But as it appeared, he only missed a gun from his collection, which he was very proud of. (One of his uncles had taken it, considering it an inheritance.) After the firearm had been replaced, he became calm again. When asked two months later about his parents, he seemed to be dimly aware of his father's death (Milner *et al.*, 1968).

This event and some additional ones demonstrate that H.M. was occasionally able to remember stimuli long-term when they were emotionally highly arousing, a phenomenon also found in other amnesic patients (Claparède, 1911; Johnson *et al.*, 1985; Markowitsch *et al.*, 1984; Meudell and Mayes, 1981; cf. also Weiskrantz and Warrington, 1979). For instance, H.M. knew that Pope John XXIII died and that President J. F. Kennedy was assassinated (Milner *et al.*, 1968).

Following his father's death he was given protected employment in a rehabilitation center during the weekdays and performed monotonous work such as mounting cigarette lighters on cardboard frames. He did not remember details of his work or the center even after six months of employment. When he was driven home one day after work, he directed the car driver to the previous address, where he had lived prior to surgery.

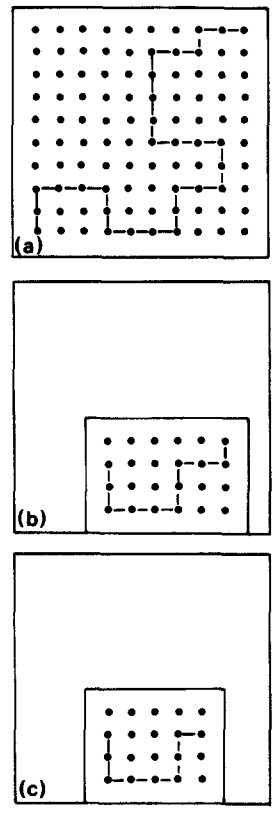

FIG. 9. Basic schemes of the so-called visual stepping-stone stylus mazes used by Milner *et al.* (1968) to test the mnemonic abilities of patient H.M. The black points are metal bolt-heads in a wooden base. The task of the subject was to find the correct way from the left to the right. H.M. and the other patients tested had to proceed from bolt to bolt, while the click of an error counter signalled mistakes. In (a) the most complex maze is shown, the pathway of which was remembered over days by brain damaged subjects, while H.M. failed to reduce his error score in 215 trials, in (b) a considerably reduced maze is shown, but H.M. could still not learn the pathway, in (c) finally a very small maze with a rather simple route is shown. H.M. acquired the pathway of this maze, but was unable to remember the way after 24 hr, while patients with other kinds of brain damage could do this without error. Milner *et al.* (1968) assumed that the pathway shown in (c) can be remembered by the capacity of a short-term store.

4.1.2.2. *The time period between 1970 and the present*

During the 1970s and 1980s H.M. took part in investigations which were intended to test newly-formed hypotheses on memory disturbances in patients with medial temporal lobe damage, or which were expected to reveal further, more subtle memory-related handicaps. The first group of experiments consisted of special variants of learning-, memory- and forgetting-paradigms (Cohen and Corkin, 1981; Freed *et al.*, 1984; Gabrieli *et al.*, 1983, 1984; Huppert and Piercy, 1982; Marslen-Wilson and Teuber, 1975; Nissen *et al.*, 1981; Sagar *et al.*, 1984) and tests of spatial orientation (Smith and Milner, 1981); the second group included tests on the perception of odors, hunger and pain (Hebben *et al.*, 1981). Corkin and co-workers (Corkin *et al.*, 1981, 1983) also observed further details in the daily life of H.M.

One test demonstrated rather well the extent to which the amnesic syndrome is characterized by the inability to acquire new information long-term in spite of intact pre-morbid memories. Here H.M. was shown the portraits of well-known individuals from different periods of his life (youth to the end of the 1960s) and he had to identify them. The outcome of this test, summarized in Fig. 10, impressively demonstrates H.M.'s well-preserved retrograde memory and, even more impressively, his lack of recent memory for the decades of the 1950s and 1960s, that is, the period following his brain damage.

In addition to his basic memory disturbances, H.M. apparently also lacked normal thresholds for certain sensations. Thus he had considerable difficulty in identifying odors

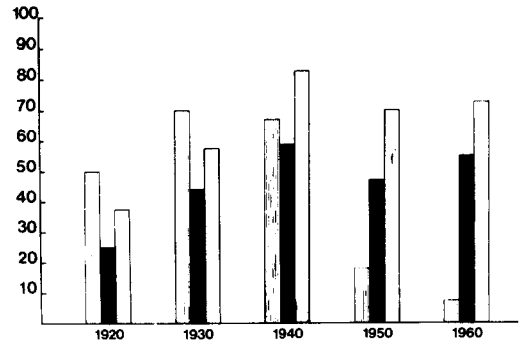

FIG. 10. Results on the "famous faces" test for H.M. (left striped columns), other brain damaged patients (black columns) and non-brain damaged control subjects (stippled gray columns). The ordinate gives the present values for currently identified individuals, the numbers at the abscissa represent the decades (1950 = decade from 1950 to 1959) in which the persons asked about were prominent.

within complex learning situations, though he was able to detect and differentiate odors (Eichenbaum *et al.*, 1983). His sensations for hunger and pain were also reduced (Hebben *et al.*, 1981), and when asked to rate his state of hunger along a scale from 0 to 100, he always responded with a 50, independent of whether it was before or after a meal, though once, when he was given a second dinner immediately after the first, he completed everything again except the salad, and then reported to have had "enough", rating his satiety this time with 75.

H.M.'s anterograde amnesia still appears to be unchanged in recent years (Corkin *et al.*, 1981). He does not know where he lives or who cares for him. In 1981 he answered questions as to the year with anything between 1958 and 1993 and he underestimates his age by 10 to 26 years. In spite of this he does have "islands of knowledge". He knows for instance that an astronaut travels through space, and that rock music is a new kind of music (Corkin *et al.*, 1981). Typical daily activities are solving crossword puzzles and watching television. In 1982 he was still able to draw a ground plan of the house in which he lived for many years following his operation (up to 1974) (Corkin *et al.*, 1983). On the other hand, he was incapable of identifying his mother in a photograph taken in 1976 on the occasion of his 50th birthday and the same holds true for a photograph of the woman who cared for him for many years (to the end of the 1970s). With one exception for 1959 he remembers popular songs only from the time period prior to his operation (Corkin *et al.*, 1983).

In the meantime, neuronal damage has appeared in addition to that caused by the surgery (as evaluated, e.g. from CT-scans), mainly peripheral neuronal damage (influencing the activities of his extremities), a cerebellar damage and a widening of his lateral fissure (Corkin *et al.*, 1981). In addition his intelligence quotient is apparently decreasing and is probably around 100 at the present (Corkin *et al.*, 1981; Smith and Milner, 1981), although this result may be in part age-dependent.

In summary then, this description of the best-known case of amnesia in the literature exemplifies where the principal memory difficulties of amnesics lie and how tests have been applied continually to elucidate the basic mechanisms involved. Although there are differences between the amnesic syndrome manifest in H.M. and that seen in Korsakoff patients (Mair *et al.*, 1979), or in others with even more discrete diencephalic damage (Case N. A.; Teuber *et al.*, 1968; Squire and Moore, 1979), the basic inability, the profound anterograde amnesia for specific (episodic) events, is similar.

In the following we will describe several additional cases with medial temporal lobe damage and resultant global amnesic states.

4.1.3. *Other cases of epileptics with temporal lobe resections and mnestic disturbances*

There are several older descriptions of patients in whom a relation between epilepsy, hippocampal degeneration and amnesia was noted. In 1880, Sommer had already

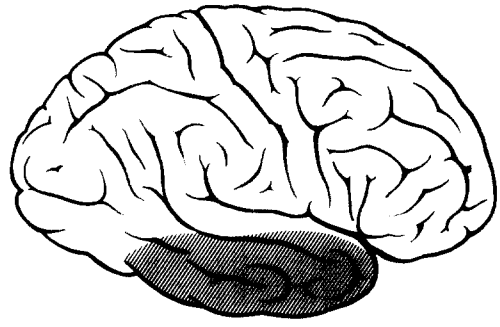

FIG. 11. Schematic view of the extent of brain damage in the patient described by Zingerle (1912). (After Fig. 1 of Zingerle (1912).) The defects enclosed the whole ventral part of the right temporal lobe from lateral to medial.

summarized the results from 90 cases with pathological changes in the hippocampus and epilepsy. From the surveyed data and from his own observations he hypothesized that Ammon's horn damage existed first and was secondarily followed by epileptic attacks. (This hypothesis was later taken up by others, while the opposite sequence of events was postulated by Scholz (1951); for a more detailed discussion of this topic see Corsellis (1970) and Dam (1982).)

Although it is a common statement that damage of (one or more) structure(s) has to be bilateral in order to result in lasting amnesia (cf., e.g. Victor, 1964; Victor *et al.*, 1961), there are a number of notable exceptions (see Blakemore and Falconer, 1967; Caplan and Hedley-Whyte, 1974; Dimsdale *et al.*, 1964; Milner, 1965, 1968; Mohr *et al.*, 1971; Penfield and Milner, 1958; Squire and Moore, 1979). One of the earliest cases mentioned in the neuropsychological literature is that of a patient with marked memory disturbances and epilepsy, and this was described in considerable detail by Zingerle (1912), who provided photographs of 17 coronal brain sections, a basal view of the whole brain and a schematic lateral view of the brain of the patient with the ventral half of the right temporal lobe totally degenerated (Fig. 11).

In the 1950s and later several reports appeared of cases frequently involving a long epileptic history and severe mnestic disturbances subsequent to uni- or bilateral excisions of temporal lobe areas (Lechner, 1958; Milner, 1970, 1972; Penfield, 1968; Penfield and Mathieson, 1974; Penfield and Milner, 1958; Scoville and Correll, 1973; Scoville and Milner, 1957; Serafetinides and Falconer, 1962; Walker, 1957). However, there are also case descriptions of epileptic patients who, after unilateral (anterior) temporal lobectomy, failed to show any lasting memory disturbances or who even improved in their general intellectual performance (Blakemore and Falconer, 1967; Glaser, 1980; Jensen and Larsen, 1979; Novelly *et al.*, 1984). If mnestic disturbances occurred in these more recent cases they were usually observed only following lobectomy of the dominant temporal lobe and appeared to be restricted to verbal memory functions (Glaser, 1980; Novelly *et al.*, 1984), and whether mnestic functions improved or deteriorated following surgery furthermore apparently depended on the degree of post-operative seizure reduction (Novelly *et al.*, 1984). Olfactory memory functions seemed to be especially affected (Eskenazi *et al.*, 1983; Rausch *et al.*, 1977; Rausch and Serafetinides, 1975).

A new neurosurgical method, the "selective amygdala-hippocampectomy", developed by Yasargil, has apparently improved the probability of stopping post-operative epileptic attacks and has led to much less pronounced or even undetectable memory impairments in these patients (Birri *et al.*, 1982; Gonser, 1983; Wieser and Yasargil, 1982).

4.1.4. *The hippocampal formation*

As the hippocampal formation is damaged in almost all cases with medial temporal lobe damage and as this region—in particular the pyramidal cells of the so-called Sommer sector—is especially vulnerable to a lack of oxygen (cf. Uchimura, 1928), the question of

whether hippocampal lesions alone are sufficient to cause lasting amnesia (Woods *et al.*, 1982) has been raised repeatedly. Probably the first affirmative answer to this question was given by Bechterew (1900). At a meeting in 1899 he showed a human brain with softening of the anterior and medial parts of both temporal lobes. The brain came from a 60-year old man who had had a very noticable weakness of memory during his last 20 years of life, and who—on the basis of the overt symptomatology—had at first been considered a Korsakoff patient (at an earlier meeting of the Russian Society for Psychiatry and Neurology).

One British and two Swiss cases with profound dementia and bilateral or unilateral destruction of the Ammon's horn were described in detail by Grünthal (1947), Hegglin (1953) and Glees and Griffith (1952).

Grünthal's case is that of a woman with mild diabetes who was hospitalized at the age of 67 due to an infection. After successful treatment she was released, but at home she suddenly fell into a hypoglycemic coma and quickly deteriorated in her intellectual level and manifested signs of a Klüver–Bucy syndrome (especially an increased oral activity). Autopsy revealed a reduced volume of the cranium and the brain. Nevertheless the principal macroscopical abnormality was a bilateral reduction in the size of the hippocampal formation. No senile plaques were found. On the light microscopical level the only serious changes again were found bilaterally in the Ammon's horns.

Grünthal emphasized that after the successful treatment of the infection (including a three month stay at the hospital) the patient was not dement, but well-oriented and reasonable and it was not until her insulin coma, which occurred three days later, that she deteriorated intellectually and furthermore that apart from the destruction of the Ammon's horn the other observable changes in the brain were age-related and could not have caused the severe intellectual deterioration.

Glees and Griffith described the case of an older woman (58 years) who had been hospitalized, however, for the 15 years before she died. During her stay she deteriorated progressively in cognitive behavior, with anterograde and retrograde amnesia being the most prominent symptoms. As in the case of Zingerle (1912) (cf. Fig. 11), a cyst occupied the region of each of the two medial and anterior temporal lobe areas, where the respective neuronal tissue was completely missing. The rest of the temporal lobe was preserved and showed "a normal cortical arrangement in layers" (p. 197). The fornix was densely gliosed (75% of its fibers were degenerated), while the amygdala appeared normal in structure as did the thalamus, hypothalamus, basal ganglia and the rest of the cerebral cortex. The authors considered the damage to be of vascular origin, but emphasized the normal appearance of the mamillary bodies, which corresponds again to Grünthal's case (and furthermore to another case with hippocampal damage and an absent fornix: Nathan and Smith, 1950). Thus, other connections of the mamillary bodies, and not just the fornix, seem sufficient to keep their neurons alive (cf. Irle and Markowitsch, 1982a; Irle *et al.*, 1984).

Hegglin's (1953) case, the third in this series, was similar to that of Zingerle (1912) in that hippocampal softening was again only unilateral and nevertheless apparently led to pre-senile dementia. On the basis of the observed sclerosis of the basal artery, Hegglin assumed that vascular damage was the origin of the insult. The 63-year old patient was observed for about three months during which time he was found to have a marked anterograde amnesia, extensive remote memory gaps and a disorientation in space and time. In his discussion of the case, Hegglin was among the first authors to ask whether an acute destruction of the hippocampus alone might be able to cause dementia (and in his case it was only a unilateral destruction of the pyramidal cells of the Ammon's horn) ("Kann eine akute Zerstörung des Pyramidenbandes eines Ammonshornes, eines relativ kleinen Teiles des Großhirnes, die beobachteten schweren klinischen Erscheinungen einer präsenilen Demenz verursacht haben?"; p. 179). While he did not have confidence enough to give a positive answer from his case with unilateral damage only, he cited Grünthal's case (and that of Conrad and Ule, 1951) as support for the likelihood that an acute, massive destruction of the Ammon's horn might result in amnesia.

While none of these cases are comparable to H.M. in showing normal aspects of intellect and personality combined with a profound recent memory disturbance, there are some more recent cases in which the nature of both the psychological and neuropathological variables could be more narrowed down.

The case of Victor *et al.* (1961) has often been considered as a particularly clear example of this, though, in fact, this case apparently did have more widespread anatomical damage. The male patient, 54 years of age, was admitted to a hospital in 1951 because of visual disturbances (hemianopia) of probably neuropathological origin. Two years later he was readmitted, but this time, in addition to the visual defects, prominent disturbances in recent memory were also found. A neuropsychological examination revealed above-average intelligence (verbal scale IQ: 117; performance scale IQ: 112), but profound impairments in forming new memories, and a fairly well-defined retrograde amnesic period which covered the time from 1951 onwards. These symptoms were re-rated on the basis of psychometric tests from 1955, and remained until his death in December 1956. Post-mortem examination of the patient's brain revealed an occlusion of both posterior cerebral arteries at a point 2 cm distal to the bifurcation of the basilar artery. Brain damage was found (mainly bilaterally) in cortical, diencephalic and midbrain regions and in the cerebellum. However, the authors considered only "the lesions [found] in the medial parts of the temporal lobes and in their projections (the fornices)...[as] responsible for the amnestic symdrome" (p. 258). (Other cortical changes were characterized as unimportant and the report considered the diencephalic and midbrain lesions to be of recent origin ["terminal lesion", p. 257].)

DeJong and colleagues (DeJong, 1973; DeJong *et al.*, 1969) presented a case in which severe memory disturbances suddenly developed, accompanied by confusion and disorientation. The memory disturbances persisted, although the patient otherwise remained within the normal intelligence range. Four months later he died after a myocardial infarction. Autopsy revealed bilateral infarcts of the hippocampi and of adjacent regions.

In four other cases with different etiologies, relationships between amnesia and dysfunction of the hippocampal regions have been made likely (Cummings *et al.*, 1984; Muramoto *et al.*, 1979; Ponsford and Donnan, 1980; Woods *et al.*, 1982). One of these, the case described by Muramoto *et al.*, seems especially interesting as the patient had a strong, persisting and selective anterograde amnesia without other signs of intellectual deterioration. Again, the neuroanatomical evidence—obtained from pneumoencephalography (but not visible in the CT-scanner used at that time)—indicated atrophic changes confined to both hippocampi.

In the case of Cummings *et al.*, the psychological defects were not so circumscribed as in the case of Muramoto *et al.* (e.g. he also had some degree of retrograde amnesia and fatigued rapidly); for this case, however, an autopsy was made which revealed "that nearly all large pyramidal cells had disappeared from the outer layers of the hippocampus and residual neurons were shrunken and pyknotic.... Neurons in the dentate gyrus were preserved, and normal neuronal population density reappeared in the subiculum and parahippocampal gyrus" (p. 679). A small infarct (5 mm) was found in the left thalamus at the junction of the pulvinar and the ventral–posterior nucleus, and another one in the right frontoparietal region. The rest of the brain basically had a normal appearance. Cummings and co-workers considered their patient as the first case in the literature with post-anoxic amnesia which was studied both clinically and pathologically.

A similar description of a patient with a hypoxic–ischemic episode (following by-pass surgery) was recently given (Zola-Morgan *et al.*, 1985). The only cognitive impairment was a memory deficit (overall intelligence: 111; Wechsler memory quotient: 91), consisting of a marked anterograde and a mild retrograde amnesia (spanning the 1 to 2 years prior to the onset of his amnesia). Again, the CA1 pyramidal cells were degenerated along their entire anterior–posterior extent (cf. Fig. 12).

While the data from all these cases stress a crucial role of the hippocampus proper for successful long-term information processing, both theoretical studies (Horel, 1978) and case reports (e.g. Gol and Faibisch, 1967; Gonser, 1983; Hyman *et al.*, 1984; Landi *et al.*,

1982; Van Hoesen *et al.*, 1985) exist which either de-emphasize its role or at least stress the importance of other temporal lobe regions. Furthermore, damage in cases with hippocampal pathology is frequently more widespread, as will be shown in the next section.

4.1.5. *Cases with more widespread temporal lobe damage*

We will only briefly mention some of those reports in which descriptions were given of amnesia accompanied by more widespread damage of temporal lobe structures, because in these cases the memory disturbances were usually only observed alongside other psychological deficits and because the cases do not allow a differentiation between specific hypotheses on critical temporal lobe areas (such as, e.g. the temporal stem or the CA1 field).

Drachman and Arbit (1966) studied five cases with known or presumed temporal lobe pathology of different origins using memory tasks. Their aim was to provide evidence for a differentiation between short-term memory (intact in this group) and long-term memory (impaired in this group), suggesting different loci for the processing of these two abilities.

Cases with larger temporal lobe lesions may have dementia (Hubbard and Anderson, 1981; Jarho, 1973; Medina *et al.*, 1977), or may show a number of emotional or other changes in addition to their mnemonic disturbances (Hierons *et al.*, 1978; Mohr *et al.*, 1971). This is particularly true for cases with damage to amygdaloid and hippocampal regions (Mehraein and Jamada, 1967; Sarter and Markowitsch, 1985a). An isolated lesion of the amygdaloid complex, on the other hand, usually only has indirect effects on long-term mnemonic information processing (Sarter and Markowitsch, 1985a; but see Andersen, 1978). Sarter and Markowitsch proposed that the role of the amygdala in information processing consists of "activating or reactivating those mnemonic events which are of an emotional significance for the subjects' life history and that this (re-)activation is performed by charging sensory information with appropriate emotional cues" (p. 19) (cf. Section 7.2.2 in which results are reviewed of studies on animals with combined amygdala–hippocampectomy).

Recently, Simpson and Swash (1985) described the case of a patient with a left temporal lobe abscess after already having one in the region of the right temporal lobe 28 years previously as a five-year old boy. This right-sided abscess had been removed during craniotomy by aspiration through burr holes, while the present one was cured pharmacologically with antibiotics and had completely resoluted after 12 weeks of therapy. During the time of the second affliction the patient developed marked memory and speech problems with retrograde amnesia even for the names of his three children, disturbances which gradually disappeared during the weeks of antibiotic treatment.

This case is reminiscent of the studies of Horel (Horel *et al.*, 1984; Horel and Pytko, 1982) in which the authors showed that temporal lobe cooling suppresses mnemonic activities.

4.1.6. *Phenomena related to electrical stimulation of the temporal lobe region*

A number of studies in which electrical stimulation of the amygdaloid region was applied (usually prior to operative resections) were reviewed by Sarter and Markowitsch (1985a). Penfield in several reports (Penfield, 1958, 1959, 1975; Penfield and Perot, 1963; cf. also Feindel, 1982), as well as others (Chapman *et al.*, 1967; Fedio and Van Buren, 1974; Feindel, 1961; Halgren, 1981, 1984; Halgren *et al.*, 1978b, 1983), described phenomena evoked by stimulation of temporal lobe regions.

The range of phenomena evoked by such stimulation is broad and may include perceptual hallucinations, memory flashbacks, illusions of familiarity (*déjà vu*), compulsive thinking or emotions (Gloor *et al.*, 1982; Halgren *et al.*, 1978b). However, while both deeply hidden memories as well as amnesia and confusion could be provoked by electrical stimulations, and may therefore deliver "a caricature of medial temporal lobe function" (Halgren *et al.*, 1978b, p. 105), the authors concluded that "the mental phenomena evoked

by medial temporal lobe stimulation are idiosyncratic and variable, and are related to the personality of the patient stimulated" (p. 110).

From their own stimulation data, Fedio and Van Buren (1974) suggested a distinction between the mnestic effects of anterior and posterior temporal lobe structures: stimulation of the anterior temporal neocortex being related to anterograde amnesia and stimulation of the posterior temporal neocortex to retrograde amnesia. Phenomena interpreted as reflecting short-term memory have been obtained as well following stimulation of lateral temporal lobe regions (Fried *et al.*, 1982; Ojemann, 1983).

Although it is not concerned with direct stimulation of the temporal area, it should be mentioned at least tangentially that recent memory-related single unit activity has been recorded (Halgren, 1984; Halgren *et al.*, 1978a).

As can be seen from this summary of the findings obtained by stimulating temporal lobe structures, the range of evokable phenomena is broad and may differ considerably in content and vividness between individuals. In addition, the frequently only limited possibility of precisely determining the locus of stimulation and the inverse possibility of rather influencing an unknown area of nerve cells by spread of current, hinder a topographical analysis and add to the diversity and variability of the phenomena. This will be the case all the more as a number of partly extensive fiber bundles exist within the stimulated region. Nevertheless, the findings taken together confirm the memory processing role of the temporal lobe and furthermore make it appear likely that the emotional significance of a stimulus determines its storage and subsequent availability to a considerable degree.

4.1.7. *Fornix damage*

The fornix constitutes the main efferent pathway of the hippocampal formation, originating largely in the subicular cortex (Irle and Markowitsch, 1982a) and terminating in the mamillary bodies (cf. Fig. 7) and the septal region of the anterior telencephalon.

The possible contribution of the fornix to mnestic information processing is a matter of particular controversy at the present. Older sources emphasized its involvement in memory on the basis of the fact that it constitutes the principal connection between those two structures which are most frequently mentioned as leading to amnesia if damaged. More recently, however, Squire and Moore (1979) stated that they found 47 cases in the literature in which surgical interruption of the anterior fornix did not affect memory functions to any noticeable degree and only three in which memory dysfunction was noted. They suggested that in those cases with memory impairment the pre-commissural fornix had been damaged, while in the others damage might have been restricted to the post-commissural fornix.

The three case descriptions with mnestic disturbance were those of Hassler and Riechert (1957), Sweet *et al.* (1959) and Heilman and Sypert (1977). The anterior columns of the fornix were sectioned in the 36-year old patient of Sweet *et al.* (1959) and this resulted in "a severe loss of memory for recent events...[which has] persisted now for two years" (p. 76). Nevertheless the difference between her memory quotient (90) and her overall IQ (103) was small, perhaps too small to be considered sufficient for amnesia, a view stressed repeatedly by Squire and co-workers (Squire, 1981, 1982a; Squire and Zola-Morgan, 1983). (We agree with this view though Squire and co-workers (Zola-Morgan *et al.*, 1985) recently presented a case of "amnesia" in which the difference between these two measures was not much higher [IQ: 111; MQ: 91].)

In the case described by Heilman and Sypert (1977) psychological and neuropathological deficits were distinct: a persistent memory disturbance (total IQ: 108; MQ: 72) and a neoplasm in the subarachnoid space of the quadrigeminal cistern which had destroyed the posterior fornix bilaterally (see the figure in Heilman and Sypert which gives the locus of the tumor). It should be noted that though this tumor generally failed to affect surrounding structures, it did involve the hippocampal commissure. (A rather speculative assumption is that some communication between the two hippocampi might be necessary for successful

long-term memory, as can be concluded from the cases with memory deficits after unilateral hippocampal damage, and that consequently the disruption of the hippocampal commissure might at least have added to the effects on information processing by fornix destruction.)

Apart from these three cases, referred to in Squire and Moore (1979), there are some additional cases with severe memory disturbances and fornix destruction (though not always as selective). From their own observations in a number of patients and from related observations, for example, by Delay *et al.* (1964) and Hassler (1967), Mehraein and Rothemund (1976) emphasized that fornix lesions may be decisive for amnesia. A similar suggestion was made by Brion *et al.* (1969), Cameron and Archibald (1981) and Schenk (1959a).

Furthermore, descriptions of several further recent cases are available in which the fornix was destroyed uni- or bilaterally together with the anterior cingulate gyri (Laplane *et al.*, 1981), the hypothalamus (Hier *et al.*, 1983) or other structures (Geffen *et al.*, 1980; Zaidel and Sperry, 1974), and in which mnestic disturbances were described. In the case of Hier *et al.* a short-term memory deficit as well as anterograde amnesia were found in combination.

On the "positive" side, the case description of Woolsey and Nelson (1975) is probably the best-known of the cases with fornix damage. Here the fornix had been destroyed bilaterally by a tumor and the mamillary bodies were atrophic, but the patient remained mentally normal until a few days before dying.

A more detailed discussion of possible relations between fornix damage and amnesia was recently given by Parkin (1984).

4.1.8. *Relations between amnesia and medial temporal lobe damage*

Taken together, the case descriptions of temporal lobe damage strongly emphasize the importance of medial temporal lobe structures for long-term information processing.

Selective medial temporal lobe damage usually has the following consequences. It leads to a profound, lasting anterograde amnesia but leaves short-term memory functions and memory for pre-morbid events largely intact. Usually the personality of the patient—including his/her emotional condition and intellect—is preserved, though more extensive lesions may result in a Klüver–Bucy syndrome (the symptomatology of which, however, tends to decrease with time).

Compared to the amnesic syndrome which usually follows the destruction of diencephalic regions, the retrograde amnesia is generally only mild and restricted, there is little evidence for confabulation or disorientation, but an intact awareness into the memory defect. Several authors emphasized the abnormally fast rate of forgetting, found by Huppert and Piercy (1978, 1979, 1982), as a distinctive characteristic. However, this result has been questioned recently on the basis of results obtained with H.M. (Freed *et al.*, 1984).

Although the causes of temporal lobe damage differ from one case to another and may include tumors and vascular changes, the majority of the cases are made up by epileptics who already had this illness from their early youth onwards. Thus, their past experiences, and the development and adaptation of their brain may differ considerably from those of amnesics with other neural damage. This holds in particular for the large number of alcoholic Korsakoff patients who in addition to their known or presumed diencephalic damage may have further, especially fronto-cortical, damage (cf. Markowitsch, 1985b). Still, however, cases with restricted temporal lobe damage such as H.M. are considered as representing "the 'ideal' amnesic syndrome" (Lhermitte and Signoret, 1976), and are called upon repeatedly to formulate hypotheses on the role of the medial temporal lobe region in memory consolidation. As the good pre-morbid and the poor post-morbid memory retrieval of H.M. argue against the idea that the medial temporal lobe permits memory retrieval of all information that is stored any place in the brain, or that it is the storage site for all memory, Squire and co-workers (1984a) proposed that this region "is required for only a limited time after learning and that its role is selective to a particular

domain of information" (p. 202). (Their assumption, of course, holds only for the processing of so-called "knowing that" information.)

More specifically, Squire *et al.* (1984) assumed the following

(1) The medial temporal region interacts with neocortical (and possibly other regions) in memory storage.
(2) Information is embodied in neocortical representations and in the interaction between the medial temporal region and neocortex.
(3) This interaction is necessary in memory storage and retrieval for a limited time period after learning of up to a few years.
(4) This interaction occurs only for certain kinds of knowledge (p. 203).

4.2. DIENCEPHALIC AMNESIA

While medial temporal lobe amnesia may implicate damage to this whole area (as in cases with massive infarcts or considerable resections), the term diencephalic amnesia is usually limited to two or three nuclear configurations: the mamillary bodies within the hypothalamus, the mediodorsal nucleus of the thalamus and as the third structure the anterior nuclear group of the thalamus which is connected with the mamillary bodies via the mamillary tract (cf. Fig. 6). In a few cases amnesia may be accompanied by damage to other nuclei such as the pulvinar (Victor *et al.*, 1971).

4.2.1. *Patients with Korsakoff's syndrome*

Patients with an alcoholic Korsakoff syndrome constitute the largest group of diencephalic cases. This syndrome is named after Korsakoff who, first in 1887 (Victor and Yakovlev, 1955) and then repeatedly (Korsakoff, 1889, 1890; Korsakow, 1890, 1891; Korsakow and Serbski, 1892), described patients with a symptom complex, for which "a derangement of memory and of the association of ideas" (Victor and Yakovlev, 1955, p. 396) was characteristic. Bonhoeffer (1901) listed the following as the four "cardinal elements" of the Korsakoff syndrome: a memory defect for current events (*Merkunfähigkeit*), retrograde amnesia, disorientation and confabulation. This sequence reflects the probability of occurrence as well. Korsakow (1890) already remarked that the memory defects may constitute the dominant symptoms with consciousness and lines of reasoning being relatively unaffected. As in the temporal lobe syndrome, patients with a Korsakoff syndrome may understand everything that is said to them, and can participate actively in conversations, but will have forgotten five minutes after lunch that they have just eaten (Korsakow, 1980, p. 701f).

More recent descriptions of the Korsakoff syndrome generally follow the characteristics given by Korsakoff and Bonhoeffer (Adams, 1969; Cutting, 1985; Delay and Brion, 1969; Horvath, 1975; Talland, 1965). Some exceptions exist, however. Liebaldt and Scheller (1971), for example, tried to differentiate the Korsakoff syndrome from the amnesic syndrome by characterizing the Korsakoff syndrome primarily as an "incorrect orientation", and as a lability in understanding the present "biographical position". For Van der Horst (1951) all symptoms of the Korsakoff syndrome can be explained by assuming a disturbed sense of time ("Störung des Zeitsinnes").

Apart from cases with a long history of extensive alcohol consumption, the Korsakoff syndrome may also be found in cases with other nutritional deficiencies (Bowman, 1939; Dreyfus, 1974; Minski, 1936; Victor and Banker, 1978; Victor *et al.*, 1971; Wechsler, 1933), or with infections (Serbsky, 1907) or in cases with brain tumors (e.g. De Reuck *et al.*, 1980; Gamper, 1929).

The profound anterograde amnesia and the—more variable—retrograde amnesia in Korsakoff patients have found ample documentation (Albert *et al.*, 1979; Butters, 1984; Butters and Cermak, 1980; Freund, 1889; Inglis, 1970; Mair *et al.*, 1979; Markowitsch, 1982a; Markowitsch *et al.*, 1984, 1986; Scheid, 1935; Talland, 1965). As was the case for patients with medial temporal lobe damage, Korsakoff patients were also called upon to test for the existence of separate short- and long-term memory stores (Baddeley and

Warrington, 1970; Brown *et al.*, 1980; Cermak and Butters, 1973; Kinsbourne and Wood, 1975). A further question which has frequently been approached by investigating Korsakoff patients is whether amnesic defects in general are due to a failure of proper encoding or proper retrieval of information. This problem has been discussed extensively in recent reviews (Butters and Cermak, 1980; Butters and Miliotis, 1985; Hirst, 1982; Knight and Wooles, 1980; Rozin, 1976; Squire, 1980, 1982a,b; Squire and Cohen, 1984). That the two positions are not necessarily contradictory was pointed out by Winocur and co-workers (1981) who referred to their own results and the studies of Fuld (1976), Huppert and Piercy (1977) and McDowell (1979) as supportive evidence for their assumption that "there is in fact mounting evidence ... that acquisition *and* retrieval are affected in the amnesic syndrome of Korsakoff patients" (Winocur *et al.*, 1981, p. 64; our emphasis).

Nevertheless Korsakoff patients may not be as ideal as some other groups of brain damaged patients for studying the mechanisms of long-term information processing, because their background and greater age usually elicit other behavioral disturbances as well which may bias, obscure or enhance the memory defect.

As to their behavior otherwise, they have been characterized as apathetic, indifferent, lacking initiative and insight into their illness, and as having a reduced state of arousal in spite of incoming stimulation (Colmant, 1965; Cutting, 1978; Mayes *et al.*, 1980; Meggendorfer, 1928; Oscar-Berman, 1978, 1980; Zangwill, 1941, 1977), and some of these behaviors are probably not solely a result of the memory defect. For example, the more general observations of perceptual and psychomotor retardation of Korsakoff patients in comparison to matched controls may be explained in part by their changed mood. Among the perceptual changes, a reduced ability in the organization of perception (Bürger-Prinz and Kaila, 1930; Oscar-Berman, 1980; Oscar-Berman *et al.*, 1973), and an impaired perceptual integration of *Gestalts* (Conrad, 1953; Talland, 1958) have been observed; and motor disturbances were obtained in the General Aptitude Test Battery (motor coordination; Tarter and Jones, 1971), and in so-called copying tests, in which symbols had to be copied in the spaces provided as quickly as possible (Glosser *et al.*, 1977).

Attentional deficits might account for the slowness in acquiring strategies (Oscar-Berman *et al.*, 1976) and the reduced sensitivity to the effects of rewards (Oscar-Berman, 1980; Oscar-Berman *et al.*, 1976), which is also manifested as a delay in the formation of stimulus-reinforcement associations (Oscar-Berman and Zola-Morgan, 1980a,b).

Korsakoff patients may have "a general limitation in the amount of relevant information they can process" (Glosser *et al.*, 1976, p. 327), which may explain at least part of their memory difficulties (cf. also Markowitsch *et al.*, 1984). Winocur *et al.* (1981), for instance, demonstrated that the introduction of appropriate cues may help Korsakoff patients to segregate new material from the old more effectively, and these findings are in line with the observation that in comparison to controls Korsakoff patients improve more when they have to recall items from a clusterable list as opposed to items from a nonclusterable one (e.g. Rubin and Butters, 1981; cf. Wickelgren's, 1979, hypothesis on this topic).

Nevertheless, several authors have emphasized that an interpretation in terms of an increased sensitivity to interference alone is insufficient to account for the generality of the memory impairments of Korsakoff patients (e.g. Butters and Cermak, 1980; Knight and Wooles, 1980). In spite of the many difficulties in interpreting this most basic deficit of Korsakoff patients, the psychological tests have confirmed and extended earlier studies from neurologists, in which this defect had been treated less extensively.

In order to show the characteristic mnestic deficits and neuropathological changes of Korsakoff patients in more detail, the two best-studied cases will be described in the following section.

4.2.1.1. *Cases of Mair* et al. (*1979*)

Mair *et al.* (1979) studied two Korsakoff patients, E.A. and H.J., over several years until their deaths at the age of 69 and 52 years, respectively.

E.A. had a five- to seven-year history of inadequate diet and excessive drinking, and H.J.

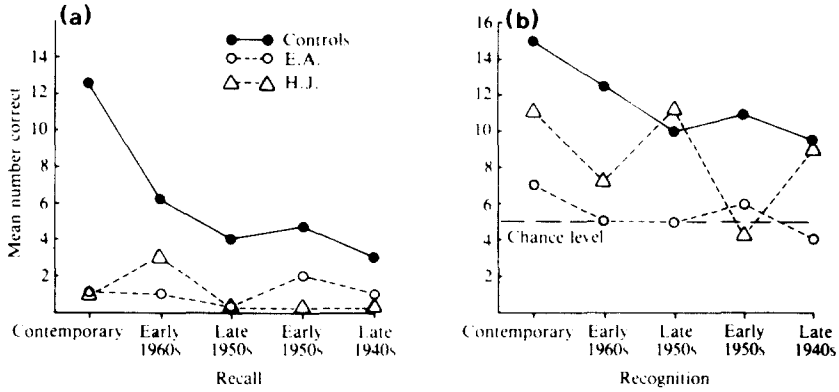

FIG. 13. Memory for well-known faces in Mair *et al.*'s (1979) patients E.A. and H.J. and in control subjects, as a function of the period during which the faces were topical, (a) recall, (b) forced choice recognition. (From Fig. 3 of Mair *et al.* (1979), reproduced with permission.)

a long history of high alcohol intake (including methyl alcohol). Both cases had severe memory deficits, but without confabulation and the patients were aware of their strong memory defects. Case E.A. had a verbal IQ of 110 and a performance IQ of 102 in 1967 and these values dropped to 94 and 88 in 1975; case H.J. had verbal IQs of 107 (1974) and 105 (1976) and performance IQs of 105 (1974) and 103 (1976). Their short-term memory (tested with digit span and Brown–Peterson paradigms) attained average or somewhat better values. The duration of their retrograde amnesia was extensive (Fig. 13), and their anterograde amnesia was particularly marked, both for verbal and nonverbal material.

Concerning the anatomical changes apparent at brain autopsy there was a surprising congruence in the damage for each of two distinct diencephalic foci: the mamillary bodies and a region between the mediodorsal nucleus and the subependymal group of nerve cells. Figures 14 and 15 illustrate the pathological findings for case E.A. and Figs 16 and 17, those for case H.J.

The mamillary nuclei were markedly gliosed, shrunken and discolored bilaterally; a gliotic tissue band was found bilaterally medial to the mediodorsal nucleus. For case H.J. these were the only pathological changes seen, while case E.A. had a small zone of softening in the cerebellum and an increased number of astrocytes in several other brain regions in addition. These data indicate that very restricted neuronal degeneration within the diencephalon may result in a full Korsakoff syndrome with severe anterograde amnesia.

However, the study of Mair *et al.* is still inconclusive as to the extensive debate on just which foci are the critical ones for amnesia when damaged: the mamillary bodies (e.g. Alling and Boström, 1980; Cravioto *et al.*, 1961; Delay *et al.*, 1958a,b; Gamper, 1928; Gudden, 1896; Harper, 1979; Orthner, 1957), or the mediodorsal nucleus (or some adjacent tissue) (Colmant, 1965; Cramon and Eilert, 1979; Kahn and Crosby, 1972; Kessler *et al.*, 1982a; Malamut and Skillicorn, 1956; Peters, 1957; Victor *et al.*, 1971; cf. also Weiskrantz, 1982a,b).

Thus, Mair *et al.* suggested that the two damaged loci might represent key stations of two memory circuits, their combined disruption being "responsible" for massive anterograde and retrograde memory deficits. (For similar propositions on the existence of parallel memory circuits see Markowitsch, 1985a; Mishkin, 1982; Warrington, 1979; Warrington and Weiskrantz, 1982; Weiskrantz, 1982b.) Interestingly, in 1928 Gamper already found several cases of Korsakoff's psychosis with a similar neuropathology.

4.2.1.2. *Other cases with Korsakoff's disease and diencephalic damage*

Since the last century it has been realized that Korsakoff's psychosis can also be present even when the brain damage is very restricted (Gudden, 1896). This damage is most

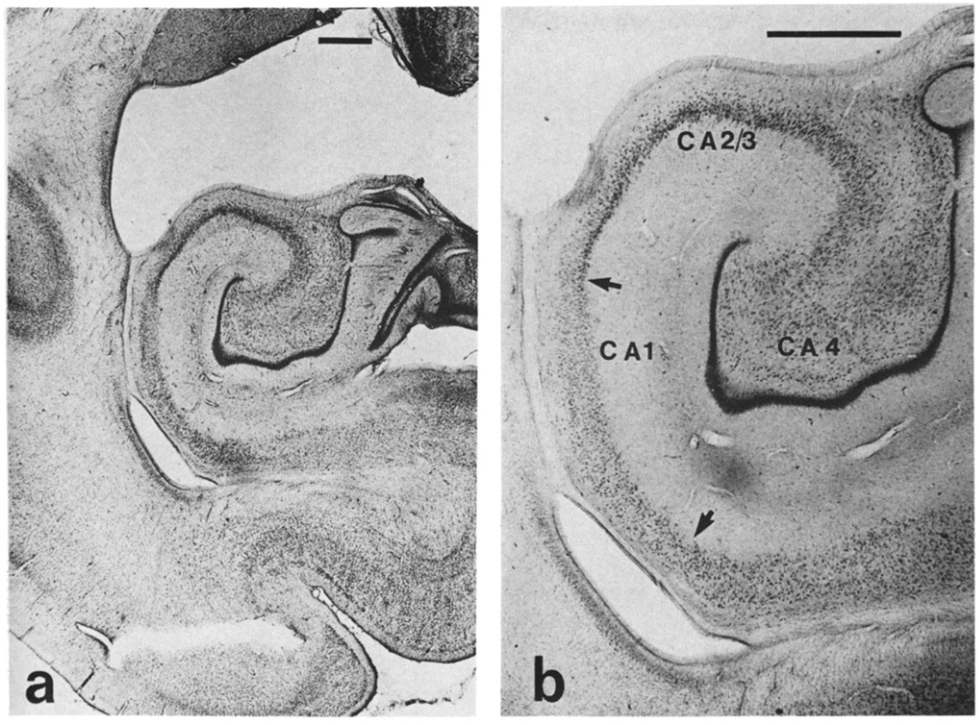

FIG. 12. A coronal section through the hippocampal region of a rhesus monkey, (a) region of the hippocampal formation under lower magnification, scale bar = 1 mm, (b) region of the hippocampus proper under higher magnification; Ammon's horn field 1 (CA1) lies within the area bordered by the two arrows, scale bar = 1 mm.

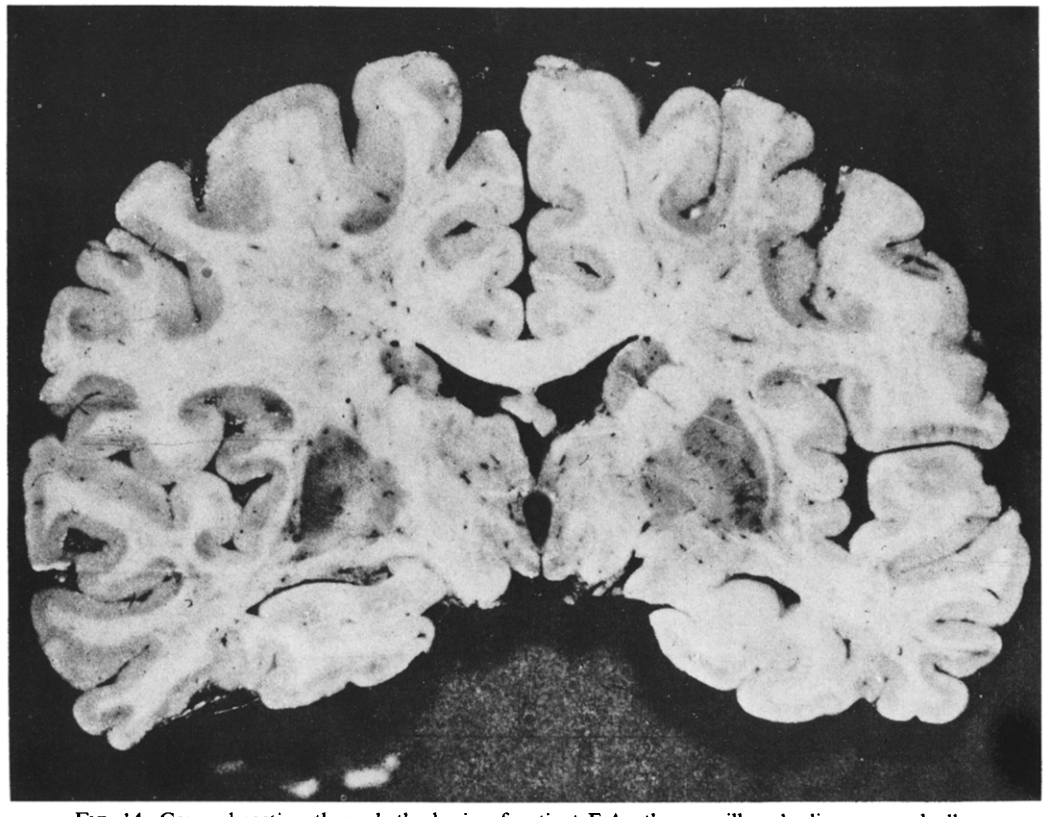

FIG. 14. Coronal section through the brain of patient E.A.; the mamillary bodies are markedly shrunken. (Reproduced from Fig. 4 of Mair *et al.* (1979), with permission.)

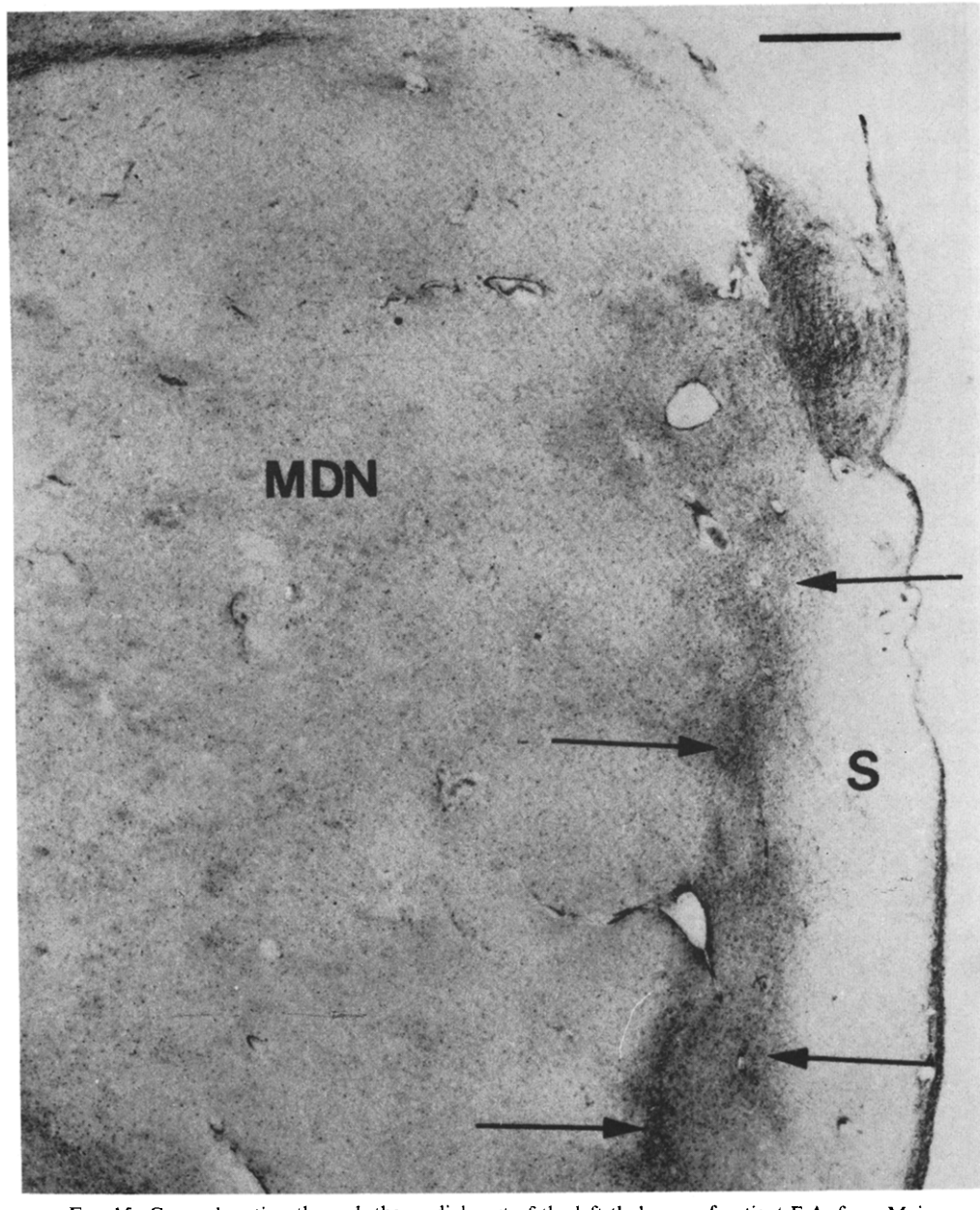

FIG. 15. Coronal section through the medial part of the left thalamus of patient E.A. from Mair *et al.* (1979). A band of gliosis (see arrows) lies between the mediodorsal nucleus (MDN) and the subependymal groups of nerve cells (S), scale bar = 1 mm. (From Fig. 8 of Mair *et al.* (1979), with permission.)

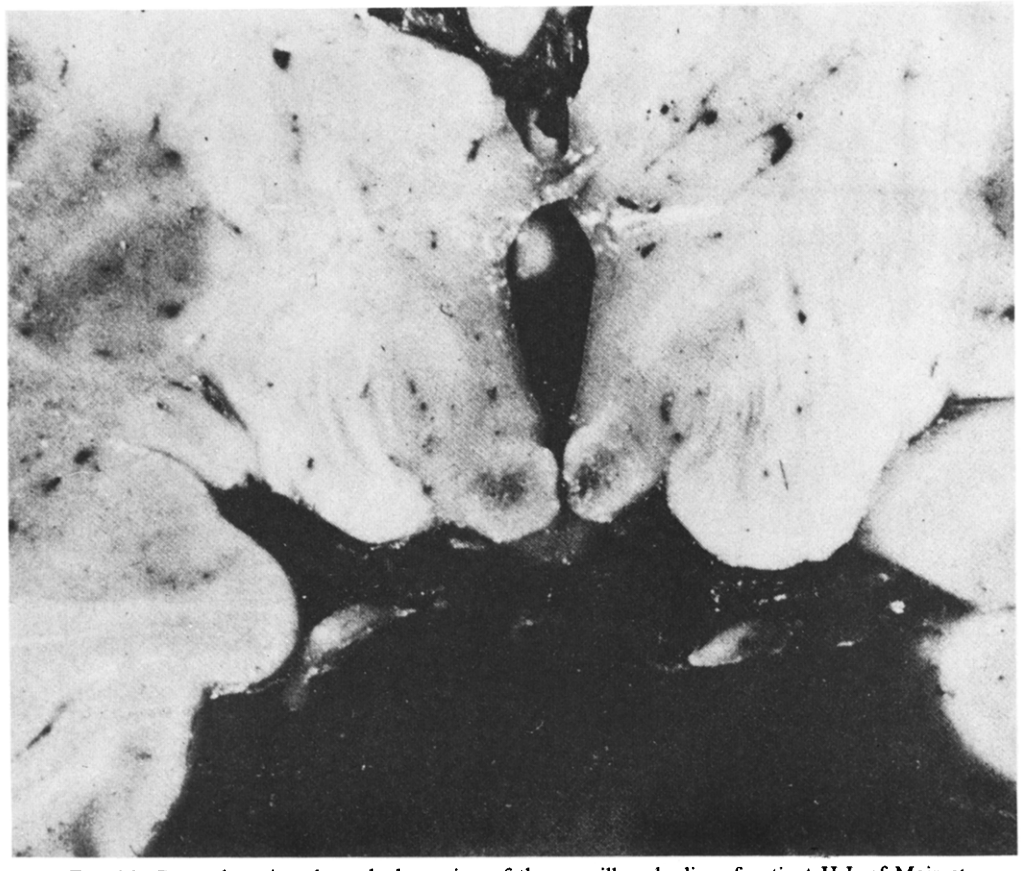

FIG. 16. Coronal section through the region of the mamillary bodies of patient H.J. of Mair *et al.* (1979). The mamillary bodies are markedly shrunken and brown in color. (From Fig. 12 of Mair *et al.* (1979), with permission.)

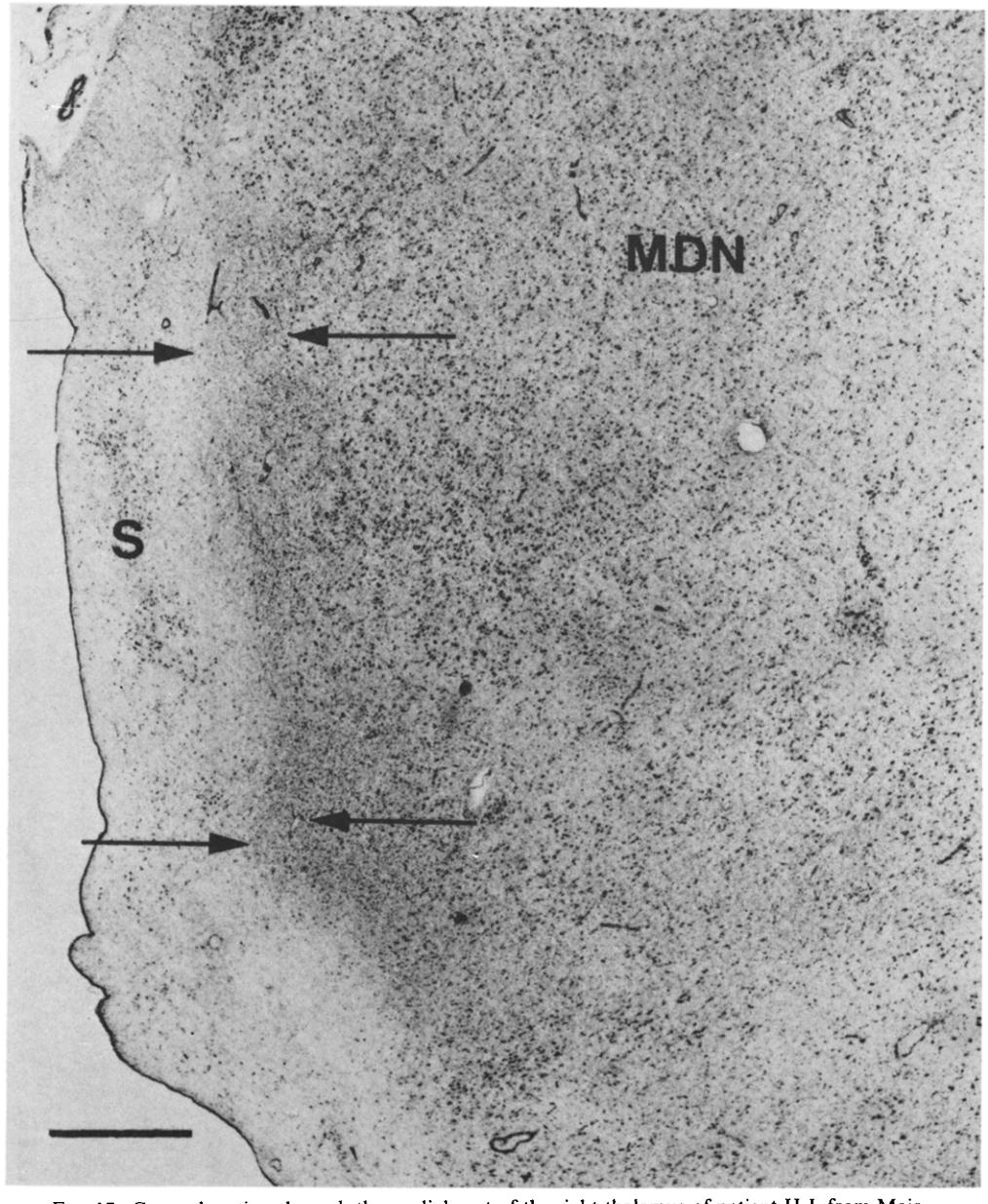

FIG. 17. Coronal section through the medial part of the right thalamus of patient H.J. from Mair *et al.* (1979). A band of gliosis (arrowed) lies between the mediodorsal nucleus (MDN) and the subependymal groups of nerve cells (S), scale bar = 1 mm. (From Fig. 15 of Mair *et al.* (1979), with permission.)

consistently limited to diencephalic structures situated next to liquor-filled space, though sometimes more diffuse cortical damage may exist as well with a preponderance in the frontal lobe (cf. Butters and Cermak, 1980; Kutner, 1906; Moscovitch, 1982; Oscar-Berman, 1984). (This may indicate an interesting relation between the liquor-adjacent brain damage and amnesia, which is seen in the fact that, in goldfish, turnover rates of certain brain proteins (ependymins) are specifically enhanced when the animals learn a new swimming behavior, and these proteins particularly are found in the cerebrospinal fluid and in the ependyma (Majocha *et al.*, 1982; Schmidt, 1983; Schmidt and Shashoua, 1981, 1983; cf. also Shashoua, 1982; cf. also Fig. 26).)

Similarly, Remy (1942) described the case of a patient who had remained stationary for 10 years and in whom a completely isolated shrinkage of the mamillary bodies was found "without any other metamorphosis in the diencephalon" (p. 144). Degenerations in the mamillary bodies (and in other regions next to the third and fourth ventricle) were also prominent in several of the 17 cases described by Kant (1932) and in several of those reported by Tsiminakis (1931), Benedek and Juba (1940, 1941) and Colmant (1965).

The study of Cravioto *et al.* (1961) has particular relevance for the possible involvement of the mamillary bodies in the Wernicke–Korsakoff syndrome. All their 28 cases, ranging in age from 32 to 82 years, showed bilateral changes in the mamillary nuclei, half of which were visible to the naked eye. (However, the thalami of all the 22 brains examined microscopically also showed damage which had not been visible without the microscope. The anterior nuclear group had been affected most consistently, the mediodorsal and ventromedial nuclei to a lesser degree.)

While these studies emphasize the role of the mamillary bodies (with or without additional thalamic involvement), there are a number of others which instead accentuate the role of thalamic structures, in particular the mediodorsal nucleus (cf. review by Markowitsch, 1982a) and which in part negate the role of the mamillary bodies (e.g. Victor *et al.*, 1971).

Victor and co-workers published a number of studies on the behavioral consequences manifest in the Korsakoff syndrome (Adams *et al.*, 1962; Victor, 1964, 1969; Victor *et al.*, 1971; Victor and Banker, 1978) and in the first of these (Adams *et al.*, 1962) they were already able to base their conclusions on the examination of more than 300 patients.

Here they stressed the critical importance of the mediodorsal nucleus (and especially its medial sector) in mnemonic processes, but it seems relevant to note that they also emphasized that "the degree of affection of fiber systems connecting temporal lobes" and other structures, among them the mediodorsal nucleus, "has not been determined, but [that] one would suppose them to be severely deranged" (Adams *et al.*, 1962, p. 275) in cases with Korsakoff's syndrome. With respect to the mamillary bodies, on the other hand, they concluded that they were unimportant for memory processing from five cases with "severe and chronic lesions of the mammillary bodies" (p. 320), none of which had manifested any memory defects, or any damage in the mediodorsal nucleus (Victor, 1964).

The description of these five cases was similar in the reports of Victor (1964) and Victor *et al.* (1971). In neither study was anything said about an additional involvement of the mamillary bodies in these patients, though one might infer from the descriptions given, that nonthalamic structures were also involved. That the mamillary bodies might have been included is suggested by the results shown in Table 28 of Victor *et al.* (1971) for a different sample of patients. Here lesions of the mamillary bodies were described in 100% of the 94 investigated brains.

In their book on the Wernicke–Korsakoff syndrome, Victor *et al.* (1971) arranged some of their findings in tables which deserve to be studied in detail. One of these findings was that memory disorders are not observed consistently in cases with a Wernicke–Korsakoff syndrome. In fact, of the 229 cases included in their Table 6, disorders of memory were found in only 131 cases (57%). Furthermore, as their Tables 3 and 16 reveal, the amnesic syndrome may show recovery. This was significant in 25% of the cases examined and actually complete in 21% (Table 16). The time periods necessary for recovery varied, however, from nine days to several years.

Among the "gross neuropathological changes in 62 cases of the Wernicke–Korsakoff syndrome" (Table 19, p. 73), 46 (74%) had lesions of the mamillary bodies and only 6 (10%) had hemorrhages of the diencephalon and/or brain stem. The mediodorsal nucleus was damaged in 38 (or 88.4%) of altogether 43 cases (Table 21), and the medial pulvinar in 17 (or 85%) of 20 cases studied. Other thalamic nuclei were also frequently involved (anterior nucleus, 35.1%; lateral dorsal nucleus, 68%; parafascicular nucleus, 50%).

Based on these results the statement is still debatable as to whether or not "as far as memory function is concerned, the important lesions are those of the medial dorsal nucleus of the thalamus rather than the mammillary bodies" (Victor *et al.*, 1971, p. 168).

Quite briefly and only for the sake of being complete we want to mention in this section the hypothesis that diencephalic degeneration in chronic alcoholics may be caused by prior liver damage ("hepatocerebral degeneration") (Kessler *et al.*, 1982a; Plum and Hindfelt, 1976; Victor *et al.*, 1965).

4.2.2. *Patients with diencephalic damage on a nonalcoholic basis*

Disturbances in blood circulation, colloid cysts within the third ventricle, tumors or system atrophy are other frequent causes of diencephalic damage. Furthermore, rare cases have been described with traumatic brain damage confined principally to the diencephalon, with probably hereditary thalamic degeneration (Kosaka and Mehraein, 1978), or with surgical lesions of thalamic structures (by electrocoagulation) (e.g. Cambier and Graveleau, 1985). Behavior and brain pathology of some of these cases appear rather similar to those in alcoholic Korsakoff's disease (e.g. McDowell and Le Blanc, 1984).

A survey of relations between damage to the mediodorsal thalamic nucleus and resultant behavioral effects (with emphasis on learning and memory disturbances) was given in Markowitsch (1982a).

Among the cases with diencephalic damage, ischemic diseases and other disturbances in blood circulation constitute the most frequent group (e.g. Choi *et al.*, 1983; Graff-Radford *et al.*, 1985; Grünthal, 1942; Kleist and Gonzalo, 1938; Langworthy and Fox, 1937). A number of case histories with thalamic softening (in most cases probably due to arterial changes) were presented in Schuster's (1936a, b, 1937a, b) four detailed "Beiträge zur Pathologie des Thalamus opticus". The damaged regions were, however, mostly asymmetrical and infiltrated several regions. In spite of substantial damage to thalamic regions, memory impairment was not among the characteristic symptoms for most of the patients.

Similarly, in the studies of Fazio *et al.* (1973), Cambier *et al.* (1982) and Walshe *et al.* (1977), memory disturbances were not among the prominent symptoms after thalamic hemorrhage. On the other hand, bilateral paramedian thalamic infarcts resulting from occlusion of a thalamosubthalamic perforating artery supplying both medial thalami (Percheron, 1976), are usually accompanied by memory disturbances (e.g. Casteigne *et al.*, 1980; Guberman and Stuss, 1983; Michel *et al.*, 1982). Michel *et al.* (1982) described a case with mild amnesia lasting two years which was apparent in a verbal memory deficiency; the patient had only unilateral thalamic damage. Guberman and Stuss (1983) described two patients with paramedian thalamic infarction, one of whom (with the more severe damage) manifested a "profound Korsakoff amnesia syndrome, and a subcortical dementia" (Abstract, p. 540). The authors included in their report a table of 13 documented cases with bilateral thalamic infarction (including their own two cases). Amnesia was present in all of them, though it was relatively mild in their own second case; symptoms of dementia were also usually present.

DeGirolami *et al.* (1974) reviewed a case with unique pathological features, namely distinct bilateral lesions in the thalamus (throughout its entire extent) and the periaqueductal gray with proliferative and inflammatory lesions in the walls of small blood vessels. The authors suggested an infective process of yet unidentified type as the possible cause. The 60-year old man deteriorated progressively in intellect and memory during the seven week course of the illness.

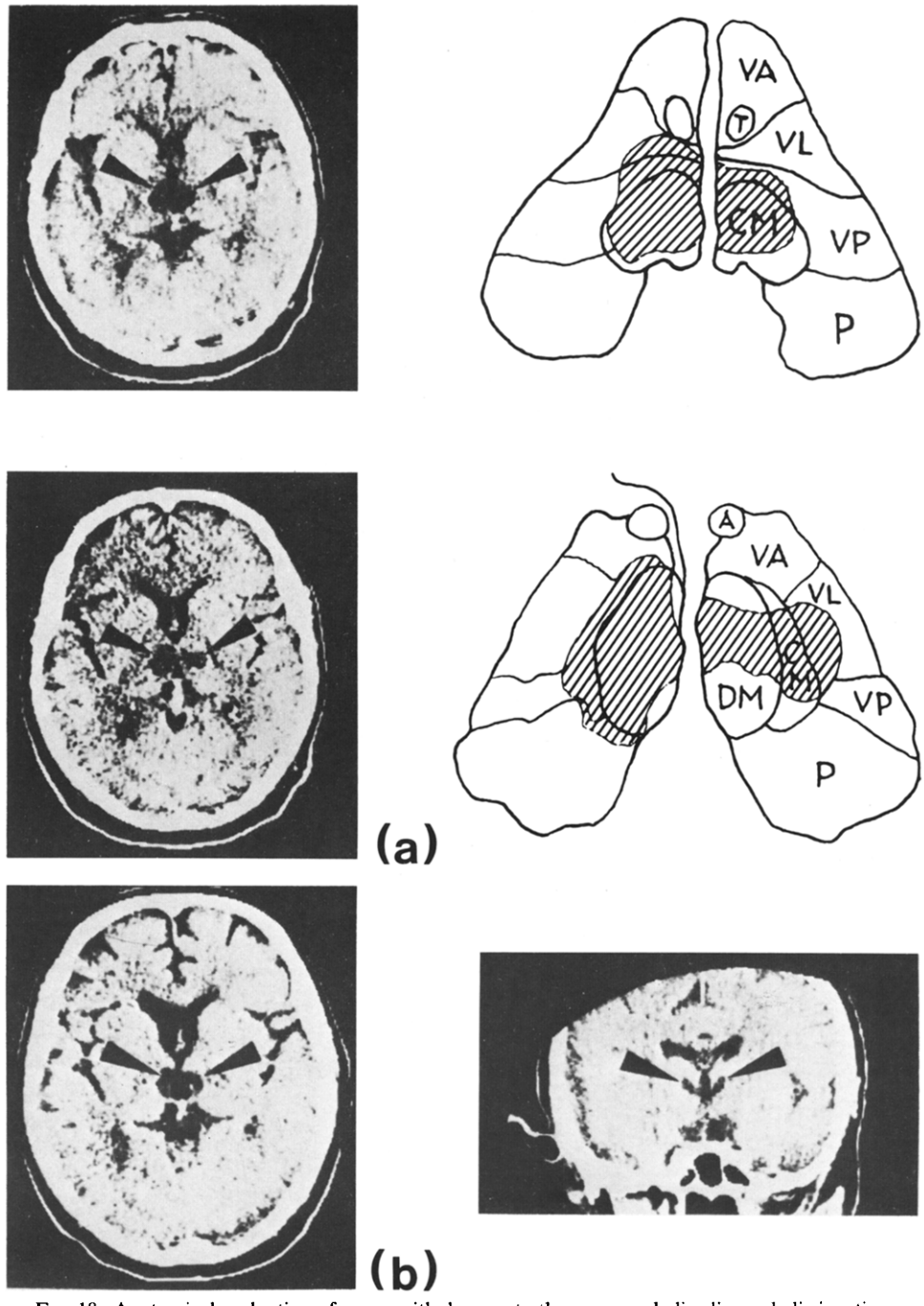

FIG. 18. Anatomical evaluation of a case with damage to the mesencephalic–diencephalic junction and memory disturbances, (A) two horizontal CT-scans with bilateral hypodense thalamic lesions (arrows) one day after the onset of the illness; the right part shows a schematic reconstruction of the lesion. Abbreviations: A, nucleus anterior; CM, centrum medianum; DM, mediodorsal nucleus; P, pulvinar; T, mamillo–thalamic tract; VA, ventral anterior nucleus; VL, ventral lateral nucleus; VP, ventral posterior nucleus, (B) control scans 10 weeks after the illness; left, horizontal section; right, coronal section. In both scans the bilateral thalamic hypodense lesion is still visible (arrows) and the third ventricle is widened. (From Fig. 1 of Kömpf *et al.* (1984), reproduced with permission.)

4.2.2.1. *Syndromes of the mesencephalic–diencephalic junction*

There are several further cases in addition to the one of DeGirolami *et al.* (1974) in which both diencephalic and mesencephalic regions were affected. Infarcts are usually the cause of this brain damage which is frequently accompanied by severe and lasting mnestic disturbances (e.g. Casteigne *et al.*, 1981; Cramon, 1980; Cramon *et al.*, 1981; Kömpf *et al.*, 1984; Mandell *et al.*, 1985). In addition, the midbrain lesion caused motor (oculomotor) disturbances. Figure 18 gives an example of the extent of such a thalamic lesion.

Casteigne *et al.* (1981) presented a list of 23 cases in their Table 5 with paramedian–thalamic and midbrain infarcts and Kömpf *et al.* (1984) gave a list of 25 cases with mesencephalo–thalamic insult in their Table 1.

4.2.2.2. *Recent cases with restricted medial thalamic lesions following ischemic damage*

In a number of cases published in the 1980s distinct thalamic lesions (with proven or assumed infarcts) were accompanied by varying degrees of memory disturbances (Goldenberg *et al.*, 1982; Graff-Radford *et al.*, 1984, 1985; Speedie and Heilman, 1982; Wallesch *et al.*, 1983; Winocur *et al.*, 1984).

With the exception of the case described by Winocur *et al.* (1984) and of two cases described by Graf-Radford *et al.* (1985), all cases had unilateral thalamic damage, which was described on the basis of CT-scans. The case of Goldenberg *et al.* (1983) was that of a 40-year old man with transient global amnesia of two day duration and a remaining retrieval deficit for "the recall of names and the information necessary to give details of particular events" (p. 79, Summary). The thalamic damage was centered towards a sector where the nuclei ventralis anterior, ventralis lateralis and mediodorsalis and the mamillothalamic tract converge (cf. Figs 1 and 3 of Goldenberg *et al.*).

Speedie and Heilman's (1982) case had a discrete lesion in the left mediodorsal nucleus and an anterograde memory impairment for verbal material. According to the authors, the patient and another one, N.A. (who had a stab wound in the left medial dorsal thalamus; cf. below, Section 4.2.2.5), showed qualitatively and quantitatively similar behavior, "and their amnesic deficit seemed less global and devastating than that of patient H.M." (p. 602).

As to the possibility that some behaviors may be lateralized at the level of the thalamus, results are still incongruent between authors. Graff-Radford and co-workers found that their three cases with left thalamic lesions had abnormalities in language, memory, visuospatial processing, intellect and personality, while their two patients with right thalamic lesions were not aphasic and had no verbal memory deficits either; otherwise they were comparable to those with lesions of the left hemisphere. The authors interpreted these results as suggesting that similar thalamic lesion loci cause a more pervasive impairment of intellect if they involve the left side.

Wallesch and co-workers (1983), on the other hand, failed to obtain evidence for such a differentiation between their six cases with left and seven cases with right thalamic lesions, although the patients with left-sided lesions performed less well in almost all tests. What these authors did find was evidence for a rostrocaudal dichotomy with rostral thalamic lesions leading rather to memory deficits and caudal lesions to impairments of "abstraction" and "categorization". The deficits, however, were not usually severe.

The case of Winocur and co-workers (1984), with bilateral lesions of parts of the mediodorsal, central and ventro-oral nuclei and the lamella medialis (cf. their Fig. 1), had a severe anterograde amnesia for both verbal and nonverbal material. (The authors assumed an infarction within the regions of the paramedian thalamic arteries as the cause of the lesion.)

Neuropsychologically, the patient was studied thoroughly on four occasions: the first on days 12, 17 and 19 after onset of the illness, and then the others six weeks, four months and eight months after the onset. His total IQ was 109 (verbal IQ: 114; performance IQ: 103) which was rather similar to his estimated pre-morbid IQ of 111. On the basis of these tests and after comparison with the results obtained on a patient with an assumed distinct

unilateral damage of the medial thalamus (case N.A.; Squire and Moore, 1979; Squire and Slater, 1978), Winocur and associates suggested that thalamic lesions disrupt the long-term processing of memory events at the initial stages of information processing. They found, for instance, that their patient performed more poorly than control subjects in a so-called Peterson and Peterson task (recalling three-letter words after intervals of 0, 3, 6, 9 and 18 sec) and manifested a faster rate of forgetting than controls.

All three cases of Graff-Radford *et al.* (1985) with medial thalamic infarction (one with unilateral, two with bilateral damage in the territory of the paramedian thalamic arteries, termed deep interpeduncular profunda arteries by Graff-Radford *et al.*) also had severe mnestic deficits which persisted for retrograde and anterograde material, as can be inferred from the patient who was retested 18 months after the infarction, although the authors considered her anterograde memory impairment as less severe than H.M.'s (see Section 4.1.2); for her retrograde amnesia they did not find a temporal gradient with respect to a famous faces test, in which patients have to identify faces from different periods of their lives. Such a temporal gradient had been found for the Korsakoff patients tested by Albert *et al.* (1979), but not in those tested by Sanders and Warrington (1971) and by Mair *et al.* (1979) (cf. Fig. 13).

4.2.2.3. *Tumors in the diencephalon*

Brain regions affected by expanding tumors cannot be described as precisely as those following, for instance, ischemic insults. Depending on the kind of tumor, its removal may lead to an enhancement of the behavioral effects present before, to no remarkable changes or even to complete recovery of functions (Foerster and Gagel, 1934; Geffen *et al.*, 1980). In the following we will describe a few selected examples which may add information on possible relations between memory disturbances and the presence of tumorous tissue in the region of the diencephalon.

Sachs and co-workers (1962) reported the results of three cases which they had investigated themselves, and summarized the results of 17 further cases from the literature with meningiomas occupying the pineal region and the posterior part of the third ventricle. Though the meningiomas were quite substantial in all three cases and though all three died a short time after the operation, memory impairments were only noted cursorily in but one of them.

Another case with an intraventricular meningioma was reported by Rodrigues and Lawson (1982). This 69-year old woman had some "difficulty with recent memory and increasing ataxia" (p. 498). A post-mortem examination revealed chronic cerebrovascular disease with multiple old cerebral infarcts and a spherical (2 cm in diameter), partly calcified, lobulated tumor located posteriorly in the third ventricle embedded in the thalamus on each side; anteriorly, it extended to the massa intermedia; the pineal gland was normal.

While in these two case reports mnestic deterioration was not specifically examined, an older study (Sprofkin and Sciarra, 1952) revealed Korsakoff-like features in three patients of whom two had cerebral gliomas with diffuse midline involvement, and the third a tumor in the posterior portion of the third ventricle. No history of alcoholism was likely for any of these cases, but mnestic disturbances (retrograde and anterograde amnesia) were still found in all three.

The diffuse damage to diencephalic midline structures resembled that found in alcoholic Korsakoff patients and the behavioral symptomatology likewise confirmed this picture. Thus, Sprofkin and Sciarra's observations reinforce the view that a somewhat diffuse diencephalic tissue destruction may lead to the symptomatology of Korsakoff's syndrome. Further support for this argumentation can be seen in the case of Assal and co-workers (1976) which had a tumor confined bilaterally to the mamillary bodies (again, diencephalic midline structures) and a severe anterograde amnesia.

Concerning the more dorsally situated thalamic midline structures, tumors here frequently cause mnestic disturbances and removing the tumor may bring recovery from amnesia up to full restitution. This was found for one of the three cases described by

Lobosky *et al.* (1984), all the cases of Foerster and Gagel (1934) and for several of the cases described in Cairns and Mosberg (1951), but not for the cases of Beal *et al.* (1981) and Burkle and Lipowski (1978).

The intimate relation between memory impairment and tumors originating from the third ventricle was already noted in 1954 by Williams and Pennybaker who reported the results of interviews on 180 patients with verified intracranial lesions. They concluded that "from whatever aspect the material ... is analysed, it indicates that impairment of memory is most frequent, pronounced and specific when the area of the brain surrounding the floor and sides of the third ventricle is damaged" (p. 121). While their analysis again sheds light on the importance of medial diencephalic structures for long-term information processing, their report as well as most of the others available on midline tumors cannot be relied upon for establishing precise anatomico–behavioral relations, due to the uncertain nature of the effects of tumorous processes.

4.2.2.4. *Cases with thalamic degeneration*

A number of reports have been published in which the results of degenerative processes limited within the diencephalon to the thalamus alone were described (cf. Martin, 1975). Usually these cases were characterized by both severe intellectual disturbances (dementia) and a symmetrical degeneration of bilateral thalamic regions (Kaiya *et al.*, 1974; Kosaka *et al.*, 1977; Oda, 1976; Schulman, 1957; Stern, 1939). Of the 13 cases summarized by Martin *et al.* (1983) (which originated from different sources) all had dementia or an amnesic syndrome as the main clinical symptomatology.

Schulman (1957) gave a very thorough and detailed description of the neuropathological changes and behavioral disturbances found in his patient. The 50-year old man, with symmetrical thalamic degeneration, developed a distinct symptomatology of intellectual deterioration, affective disturbances, limited attention span and "bizarre features in his general behavior" (p. 449). Anterograde memory disturbances were especially apparent. He died approximately six months after the onset of the illness. Neuropathologically, the thalamic blood vessels appeared normal, as did those of the remainder of the brain. The thalamic structures with severe degeneration were the mediodorsal, lateral posterior, lateral dorsal, reticular, ventral posteromedial (ventral portion) and pulvinar (pars oralis) nuclei. The medial, magnocellular, part of the mediodorsal nucleus was, however, preserved. This fact is emphasized here as the roles of the medial (magnocellular) and the lateral (parvocellular) portions of the thalamic mediodorsal nucleus in long-term mnemonic information processing are a matter of some controversy in the literature at present. While Markowitsch (1982a) and Martin *et al.* (1983) stressed the importance of the lateral portions, Mair *et al.* (1979) (see Section 4.2.1.1) found that for their two amnesic cases thalamic damage was confined to a region adjacent to the magnocellular mediodorsal nucleus and, from a theoretical point of view as well, Horel (1978) emphasized the role of the magnocellular sector.

Areas of severe, moderate or mild thalamic degeneration are shown in Fig. 1 of Schulman (1957). From his own case and from one described by Stern (1939) he concluded "that bilateral extensive destruction of the thalamus does, in fact, lead to dementia" (p. 464), a conclusion for which apparently little counterevidence exists from human cases. (For nonhuman cases with extensive thalamic damage see Pritzel and Markowitsch, 1980.)

Three recent case reports with thalamic degeneration again demonstrate thalamic degeneration and the accompanying loss of mnemonic abilities (Hori *et al.*, 1981; Martin *et al.*, 1983; Pilz and Erhart, 1981).

Pilz and Erhart described a patient who died at the age of 61 after an illness of 20 years duration. The behavioral symptomatology was broad, including apraxia, disorientation for time and space, visual hallucinations, apathy, inertia, emotional lability, loss of memory and progressive dementia. In the thalamus neuronal loss and gliosis were seen in anterior, medial and posterior portions, the lateral regions being somewhat better preserved. In addition to these changes, damage was observed in the lateral amygdala, and in the cortex

widespread moderate degeneration of the third and fourth layers was seen. In addition, moderate atrophy was found in the vestibular nuclei, the inferior olives and the cerebellum.

Likewise, in the case of Martin *et al.* (1983), that of a 21-year old patient, several thalamic nuclei were affected, the anterior and mediodorsal nuclei strongly so, but the nuclei pulvinaris, ventralis anterior, reticularis polaris and dorsalis superficialis were also damaged, though to a lesser extent. A severe memory loss and progressive dementia developed over a period of three years, forcing the patient, who had been an excellent pupil until then, to leave high school. These memory disturbances included pre-morbid as well as post-morbid aspects. The authors suggested that the involvement of the formatio anterior and the parvocellular part of the mediodorsal nucleus could explain the prevalent and severe memory loss. They related the dementia to degeneration of the large thalamic association nuclei.

Finally, Hori and co-workers (1981) described the case of a 43-year old Japanese who struck his head against the windshield in a minor car accident, and then developed forgetfulness, psychomotor slowing and the symptoms of Korsakoff's disease. He died nine months following the onset of the stmptoms at which time autopsy revealed thalamic degeneration, as shown in Fig. 1 of Hori *et al.* The anterior and mediodorsal nuclei were damaged most severely and this was bilaterally symmetrical. However, the authors considered the trauma as releasing, not causing the illness.

4.2.2.5. *Induced thalamic lesions*

Circumscribed lesions of thalamic nuclei have been performed as a surgical treatment for the relief of pain (Hassler and Riechert, 1959; Mark *et al.*, 1960; Sano *et al.*, 1966; Spiegel and Wycis, 1953; Sugita *et al.*, 1972); for the control of aggressive behavior (Nadvornik *et al.*, 1973; Poblete *et al.*, 1970) and epilepsy (Wada, 1951; Wada and Endo, 1951); and in order to cure patients of compulsive disorders (Hassler and Dieckmann, 1967, 1973, 1976; Hassler and Riechert, 1954, 1961; Spiegel *et al.*, 1948, 1951, 1953; Wada, 1951; Wada and Endo, 1951).

All these operative interventions were intended to influence the emotional behavior of the patients, with the result that descriptions of the psychological outcome were mainly concerned with success or failure in changing the symptoms. Memory-related changes after surgery were seldom reported, although several case reports emphasized precisely the lack of any enduring memory disturbance in their patients. Wycis (1972) directly stated that "there were no untoward symptoms, evidence of confusion, inertia, or amnestic reactions" (p. 115) following one-stage bilateral stereotaxic lesions of the mediodorsal nucleus and the internal medullary lamina. Likewise, the patients became reoriented in time and space usually within less than one week following surgery, or became so immediately after the operation.

Short amnesic syndromes, however, were observed by Hassler and Dieckmann (1967). One patient manifested partial disturbances in time orientation and recent memory for six weeks following coagulation of the mediodorsal nucleus and the medial lamina on the other hemisphere, but these authors attributed the temporary amnesia of this patient to the destruction of the mamillo–thalamic tract. On the other hand they found a "severe amnesia" (p. 210) in two of six patients following bilateral coagulation of the mediodorsal nucleus and the rostral intralaminar nuclei (Hassler and Dieckmann, 1973), but they provided no description for the further course of the amnesic state.

Spiegal and co-workers (1955, 1956) considered disorientation in time ("chronotaraxis") to be a characteristic symptom of the first weeks following mediodorsal thalamotomy: "Chronotaraxis is characterized by an inability to identify the date; the patient may not know the time of the day, may make incorrect statements regarding the season of the year though this is obvious if he looks through the window" (Spiegel *et al.*, 1956, p. 97). Though they considered this symptom to be similar "at least in some respects" (Spiegel *et al.*, 1955, p. 771) to Korsakoff's syndrome, they emphasized that contrary to the Korsakoff syndrome, chronotaraxis generally lasted only a few days or weeks and only in one case was it found to endure for half a year.

Orchinik (1960) tested 46 of the patients thalamotomized by Spiegel and co-workers with a standardized memory test (Wechsler Memory Scale) pre- and post-operatively. Though the patients declined significantly within the first two months following surgery, they regained pre-operative scores when retested three months to one year after the operation.

In the majority of the studies in which stereotaxic lesions of the mediodorsal nucleus were performed, considerable improvements were noted after recovery from the operation. Disorders in memory, when present, were found to disappear within a short time, with the possible exceptions of only the two cases of Hassler and Dieckmann (1973), referred to above.

Thus it appears that even bilateral coagulations of the mediodorsal thalamus and the surrounding internal medullary lamina are not a sufficient pre-condition to establish long-lasting memory defects in humans.

Similarly, bilateral coagulation of the anterior thalamic nuclei fails to result in lasting amnesia, although mnemonic disturbances may be found for a duration of about three weeks (Mark *et al.*, 1970). On the other hand, patients with already existing damage in the central nervous system may manifest enduring amnesia, even when the induced lesion is restricted to the left ventrolateral and posteroventral nuclear masses. This was shown for two cases with Parkinson's disease (Watkins and Oppenheimer, 1962).

Furthermore, N.A. is a case in point for a restricted lesion of, apparently, mainly the medial dorsal thalamus (cf. Section 3.4.1) and has been investigated in great detail both neuroanatomically (Squire and Moore, 1979) and psychologically (Cohen and Squire, 1980, 1981; Kaushall *et al.*, 1981; Squire, 1981, 1982b; Squire and Slater, 1978; Teuber *et al.*, 1968). At the age of 22 in 1960 he sustained a stab wound from a miniature fencing foil. The foil entered the right nostril and penetrated the brain apparently up to the area of the left medial dorsal thalamus. (The figure given in the article of Squire and Moore (1979) provides a view of the approximate locus of the lesion.)

A detailed psychosocial report on N.A. (whose IQ was calculated to be 124) was given by Kaushall and co-workers (1981). Primarily N.A. is anterogradely amnesic for verbal material (Cohen and Squire, 1980, 1981): "For example, he forgets lists of words and connected prose more readily than faces or spatial locations" (p. 243; Squire, 1982a), although his remote memory appears to be unaffected (Squire, 1982a) and in fact was described as being rather good (Squire and Slater, 1978). Nevertheless, some deficits in memorizing pre-morbid events were found, but they were not considered to be due to the same kind of retrograde amnesia found in other amnesics, for example, Korsakoff patients (Cohen and Squire, 1981).

Squire (1982b) compared the performance of N.A. to that of alcoholic Korsakoff patients, and to patients who were receiving bilateral electroconvulsive therapy, as well as to depressed patients, alcoholics and normal control subjects. He found that N.A. did not exhibit certain deficits typically seen in Korsakoff patients, in particular he had no difficulty in exhibiting release from proactive interference, and no impairment in making judgements about the temporal order of recent events. Squire explained this outcome in line with the suggestions of others that Korsakoff patients have brain damage in areas outside the diencephalic one (cf. Moscovitch, 1982).

4.2.3. *Relations between amnesia and diencephalic damage*

Compared to the label "medial temporal lobe damage", "diencephalic damage" can be more widespread and diverse, due to the heterogeneity of its possible causes, the inter-connections of the diencephalic structures, the number of nuclear configurations within the thalamus, subthalamus and hypothalamus, and due to the unique position of the diencephalon between the phylogenetically old structures of the brainstem and the younger telencephalon, which especially in the human species expanded considerably.

Consequently, diencephalic amnesia is usually less "pure" than medial temporal lobe amnesia. On the one hand it may be less grave when indeed only small regions are affected selectively (examples being N.A. and the cases with surgically induced thalamic lesions),

on the other hand, it may be "surrounded" by a number of additional symptoms so that the resulting complex has to be termed "dementia". For such cases damage is known or assumed to include cortical and/or midbrain regions (around the periaqueductal gray; cf. Section 4.2.2.1) as well. Although Korsakoff patients have been described with rather circumscribed damage confined to the diencephalon (cf. case H.J. in Mair *et al.* (1979) summarized in Section 4.2.1.1), they usually manifest damage in addition to that of diencephalic structures. Furthermore, it can be assumed that even in cases with circumscribed damage confined to a thalamic nucleus or to the mamillary bodies, anterograde and retrograde neuronal degeneration has occurred as well though it may be detectable only occasionally (as in the case of Goldenberg *et al.*, 1983; cf. also Rose, 1936).

However, since amnesic symptomatology has been observed following damage to hypothalamic regions, to medial or anterior thalamic nuclei or to neuron assemblies which even defy a precise classification (as in the two cases of Mair *et al.* (1979) with respect to thalamic damage), and since in other cases no lasting amnesia was found following comparable diencephalic damage, it would be illusory to attempt a categorization of the findings with the aim of obtaining precise structure–function relations.

The prominent amnesic effects of damage to the small mamillary nuclei are especially surprising and have been associated with their position and connections. Lhermitte and Signoret (1972, 1976) and Ule (1958), for example, assumed them to be a connecting link between the hippocampal and the diencephalic memory systems. While this view emphasized a dichotomy between two systems, one connecting the hippocampus with the mamillary bodies via the fornix, and the other connecting the mamillary bodies with the anterior thalamus via the mamillo–thalamic tract, ending in the anterior thalamus as the principal path of output, present day neuroanatomy has shown that the fuller pattern of input–output relations for the mamillary bodies is more complicated (e.g. Irle and Markowitsch, 1982a; Irle *et al.*, 1984) and thus allows the consideration of these nuclei as more of a functional unit in themselves.

Apart from connectivity pattern, damage in diencephalic structures might occasionally be explained by the fact that damaged diencephalic regions are frequently situated close to the meninges and the possibility that ionic and other alterations in the liquor interact with changes in neuronal tissue (cf. Section 4.2.1.2; Kleist, 1934; Schmidt and Shashoua, 1981, 1983; Störring, 1938).

As with cases of medial temporal lobe damage, lasting amnesia may be observed even following unilateral lesions (case N.A.), though the full-blown symptomatology is much more likely to appear in cases with symmetrical bilateral damage. In fact, a certain degree of functional asymmetry has been specifically shown to exist for the thalamic level (e.g. Graff-Radford *et al.*, 1984; Ojemann, 1977; Speedie and Heilman, 1982, 1983).

4.3. Cases with other Brain Lesions and Amnesia

While the cases with medial temporal lobe or diencephalic damage are clearly the most frequent and best-known of those involving localized brain damage, some other cases of amnesia have been described with circumscribed or diffuse brain damage in other regions of the brain (cf. Butters, 1985).

When anterograde amnesia is the most prominent symptom, the damaged focus is usually within the telencephalon (e.g. Damasio *et al.*, 1985a,b), while for retrograde amnesia as the principal symptom, the damaged region is usually within the midbrain (Goldberg *et al.*, 1981, 1982). As retrograde amnesia is dealt with separately in Section 6, we will concentrate here on those cases in which anterograde amnesia is the primary deficit or in which there are more severe symptoms approaching a dementic state.

Among the regions which can be mentioned here are the septum and the amygdala. Although they are not included in the Papez circuit (Papez, 1937; Irle and Markowitsch, 1982a), they are still considered as belonging to the limbic circuit (whose structures are centrally implicated in long-term memory processing). (Possible relations between memory disturbances and amygdaloid damage were considered in Section 4.1.) As to the medial

septal region and neighboring areas, they have been combined into the "telencephalic cholinergic system" (Hedreen *et al.*, 1984; Mesulam *et al.*, 1983, 1985; Wainer *et al.*, 1984). It was recently proposed that degeneration (or dysfunction) of the cholinergic neurons of the basal forebrain is one of the main causes of Alzheimer's disease (Arendt *et al.*, 1983, 1985; Bird *et al.*, 1983; Coyle *et al.*, 1983; McGeer *et al.*, 1984; Rogers *et al.*, 1985; Whitehouse *et al.*, 1981). As basal forebrain neurons have rather widespread projections throughout the cerebral cortex (e.g. Irle and Markowitsch, 1984b,c; Mesulam *et al.*, 1983), and as Alzheimer's disease is usually accompanied by rather far-reaching degeneration of cortical and other telencephalic regions (such as, e.g. the hippocampal formation), we will deal with this group of patients separately in Section 4.3.2.

The basal forebrain region, however, is of interest not only because of its cholinergic neurons, but also because of the anterior communicating artery which, when affected, may disturb the normal activity of the surrounding neuronal tissue and thereby lead to an amnesic symptomatology (Alexander and Freedman, 1984; Gade, 1982).

Apart from the basal forebrain areas, damage to the basal ganglia or to circumscribed regions of the cerebral cortex may be followed by memory disturbances (or by dementia) (Benson, 1983; Butters *et al.*, 1978; Caine *et al.*, 1977; Cummings and Benson, 1984; Fisher *et al.*, 1983; Mayeux *et al.*, 1983; Mayeux and Stern, 1983; Neumann and Cohn, 1967; Weingartner *et al.*, 1979). In cases with damage of the basal ganglia, the mnemonic deficits clearly differ from those seen in cases with medial temporal lobe or diencephalic damage (cf. Martone *et al.*, 1984; Mishkin *et al.*, 1984; Pandya and Yeterian, 1984) and in cases with very limited cortical damage the mnestic deficits are usually circumscribed as well, causing only impairments within one modality or for a certain type of material (e.g. visual anomia, color anomia, prosopagnosia; Damasio, 1985a; Damasio and Damasio, 1983; Davidoff and Ostergaard, 1984; McCormick and Levine, 1983; Varney and Digre, 1983; Warrington and Shallice, 1969, 1984; Williams and Pennybaker, 1954).

4.3.1. *Cases with basal forebrain damage*

As stated above, there are principally two groups of patients with basal forebrain damage, those with neuronal degeneration and Alzheimer's disease and those with vascular damage (Alexander and Freedman, 1984; Corkin, 1982; Damasio *et al.*, 1985b; Gade, 1982; Volpe and Hirst, 1983b). The cases with Alzheimer's disease are, however, much more variable in their neuropathology and decline in intellectual functions progressively during the course of their illness. For this reason they will be treated separately.

4.3.1.1. *Abrupt damage of the basal forebrain*

In 1982 Gade summarized the outcome of neuropsychological examinations in 48 patients with aneurysms of the anterior communicating artery. He found that trapping the aneurysm resulted in an amnesic syndrome in 9 out of 11 patients while ligation of the neck of the aneurysm did so in only 6 of 37 patients (cf. his Fig. 1). The memory defect was usually severe and lasting, and constituted the principal defect observed. Examination of the patients two years after the operation revealed no or only minor improvements. Gade suggested that the trapping technique, especially, resulted in the disruption of the blood supply through the dorsal perforating branches of the anterior communicating artery and consequently caused neuronal degeneration in the region of the basal forebrain (Fig. 19).

Rather similar observations were reported by Alexander and Freedman (1984), for 11 patients who manifested amnesia and personality changes after surgical repair of ruptured aneurysms in the anterior communicating artery. The authors listed the medial septal nuclei, the paraventricular nucleus of the anterior hypothalamus and the medial forebrain bundle as the regions most likely affected. While eight patients were tested within six weeks of surgical treatment, three additional patients were seen 5 to 11 years following surgery. Although several symptoms present at the beginning disappeared within weeks, the anterograde amnesia persisted. Retrograde amnesia, on the other hand, lasted between one

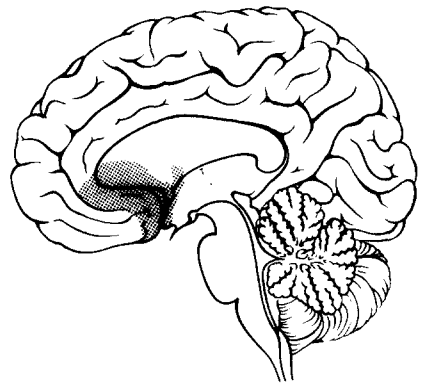

FIG. 19. Parasagittal section through the human brain. The area of neuronal degeneration is marked in the basal forebrain after rupture of the aneurysms in the anterior communicating artery. (Modified after Fig. 4 of Alexander and Freedman (1984).)

week and less than three months in eight patients, but extended to about 20 years in three others (cf. Table 2 of Alexander and Freedman for a detailed listing of clinical behaviors, affect, confabulation and for the results in formal neuropsychological tests).

Damasio *et al.* (1985b) studied five patients, four with basal forebrain lesions secondary to rupture of anterior communicating artery aneurysms, and one with a lesion caused by a resection of an arteriovenous malformation; they considered the symptomatology found in their patients, which was similar to a Korsakoff syndrome, as due to a secondary malfunctioning in the hippocampal system.

There are several somewhat older reports on relations between memory disturbances and damage to the region of the medial septum and/or the anterior cingulate cortex, confirming the descriptions given above (Barris and Schuman, 1963; Laplane *et al.*, 1981; Lechi *et al.*, 1975; Lindquist and Norlen, 1966; Talland *et al.*, 1967; Whitty and Levin, 1960; Zeman and King, 1958).

4.3.1.2. *Alzheimer's disease*

Instead of going into detail about the very large number of recent case descriptions emphasizing relations between damage to the cholinergic forebrain and Alzheimer's symptomatology, we will limit the discussion here to a few aspects. Alzheimer's disease ultimately affects most personality traits, but (verbal) memory disturbances belong to the earliest and to the most outstanding symptoms (Albert and Moss, 1984; Loring and Largen, 1985; Ober *et al.*, 1985; Rosen, 1983; Wilson *et al.*, 1983). While these mnestic changes might be related to degenerative processes in the basal forebrain, this view has not been universally accepted, as Alzheimer's disease is accompanied by changes in the cerebral cortex and in other telencephalic regions as well, including the hippocampal formation and the amygdala. Furthermore, structure–function relations on Alzheimer patients are complicated because the underlying causes of the disease are not well known and may differ between individuals (cf., e.g. the works edited by Corkin *et al.*, 1982; Katzman *et al.*, 1978; Reisberg, 1984; Albert, 1984a, and in the last mentioned book especially the chapter by Kemper).

Generally, the main focus of cell degeneration is found in the basal forebrain (e.g. McGeer *et al.*, 1984; Rogers *et al.*, 1985; Tagliavini and Pilleri, 1983; Whitehouse *et al.*, 1983; Wilcock *et al.*, 1983), but there are reports of cell loss in patients with senile dementia of the Alzheimer type in the locus caeruleus (e.g. Mann *et al.*, 1984; Tomlinson *et al.*, 1981); the striatum and diencephalon (e.g. Rudelli *et al.*, 1984); the hippocampal formation (e.g. Hyman *et al.*, 1984; Probst *et al.*, 1983), and other regions of the limbic system (e.g. Herzog and Kemper, 1980; Hooper and Vogel, 1976; Van Hoesen *et al.*, 1985); in the nucleus raphe dorsalis (Curcio and Kemper, 1984); in the cerebellum (Aikawa *et al.*, 1985) and, as expected, in neocortical areas (e.g. Cook *et al.*, 1979; Foster *et al.*, 1983, 1984; Hubbard and Anderson, 1981; Wilcock and Esiri, 1982).

Furthermore, other neurotransmitter systems, not just the cholinergic system, are also affected (Mountjoy *et al.*, 1984; Nyberg *et al.*, 1985; Perry, 1984a; Rossor *et al.*, 1982; Yates *et al.*, 1983; Zimmer *et al.*, 1984). Another difficulty for developing a general picture of the pathology behind the disease can be seen in the fact that, although the basal forebrain is so often afflicted, Henke and Lang (1983) found no significant change in choline acetyltransferase activity in a basal forebrain area, the basal nucleus of Meynert, in Alzheimer patients as compared to non-neuropathological controls, and Pearson *et al.* (1983) similarly found no differences in the number of neurons in this nucleus in patients with the disease as compared to those of age- and sex-matched normal brains, though the cells were substantially smaller in the patients' brains. The appearance and persistence of these shrunken cholinergic neurons were similar to those seen in a study in which cortical lesions in rats led to retrograde cellular degeneration in the nucleus basalis area (Sofroniew *et al.*, 1983), suggesting that cortical degeneration might be the primary event in Alzheimer patients, with an affection of basal forebrain neurons being secondary.

Support for such a view came from a study which measured the regional cerebral glucose metabolism (an index of neuronal activity) in 20 patients with Alzheimer's disease and matched control subjects (Foster *et al.*, 1984). In this report it was found that a substantial decline in glucose metabolism already occurs before cognitive impairment becomes evident.

Finally, the progressive intellectual deterioration in Alzheimer patients constitutes a major handicap against correlative neuropsychological–neuropathological studies. Consequently, there is a lack of well-controlled studies with neuropathological substantiation, with first approximations coming from Veroff *et al.* (1982) and Corkin (1982). Veroff and co-authors worked with four Alzheimer patients aged between 55 and 65 years who had a three- to six-year course of gradually progressive impairment of memory, abstract thought and other intellectual capacities, without a state of profound impairment; they administered the Wechsler Adult Intelligence Scale and the Wechsler Memory Scale and furthermore examined the brains with the help of CT-scanning. The authors found that the Alzheimer patients—compared to patients with Huntington's disease—had significantly greater CT attenuation values, and that the left temporal lobe CT values of the Alzheimer patients had significant negative correlations with the verbal IQ of the Wechsler Adult Intelligence Scale.

Corkin (1982) addressed the question of "whether the deficits in learning and remembering shown by amnesic patients with pathology in the medial temporal zone and related structures are like or unlike the patterns of memory loss seen in Alzheimer's disease" (p. 149). For the study she employed 15 elderly healthy subjects, 28 patients with Alzheimer's disease and five global amnesics. One of these was H.M. (cf. Section 4.1.2), two had ruptured anterior communicating artery aneurysms, one herpes simplex encephalitis (which may cause bilateral destruction in the medial temporal region; cf. Section 4.3.2.2) and the fifth was assumed to have a similar neuropathology owing to a cardiac arrest lasting 4–10 min at the age of 20 years. Three short-term retention tests were given (digit span, block span, a Brown–Peterson distractor paradigm), a verbal recognition memory test (assumed to measure encoding processes) and three tests for measuring learning processes (a verbal and a nonverbal paired associate learning task and Gollin's incomplete pictures test; see Fig. 3).

With this battery Corkin revealed that patients with Alzheimer's disease were impaired in both capacity and forgetting measures of short-term memory while global amnesics were not. With respect to verbal recognition memory the results were somewhat mixed, with two global amnesics behaving similarly to normals, while the other three were comparable to the Alzheimer patients. Alzheimer patients were especially weak in paired associate learning and in the incomplete pictures test compared to the other groups, and, furthermore, the degree of their impairment was directly related to the severity of their dementia.

Although the global amnesics differed from the Alzheimer patients not only in the etiology of their illness, but also in age, these data show that Alzheimer patients are more

broadly impaired in mnemonic functions than the so-called global amnesics. This finding is in line with the assumption of multiple brain damage in cases with Alzheimer's disease.

4.3.2. *Cases with primarily cortical damage*

Apart from cases with Alzheimer's disease, a number of further illnesses are known which lead to cortical damage and to mnestic disturbances. Many of these diseases have a very progressive nature and ultimately result in dementia (Alexander and Geschwind, 1984; Benson and Blumer, 1982; Haase, 1978; Joynt and Shoulson, 1985; Perry, 1984b; Roos and Johnson, 1978; Strub and Black, 1982; Tomlinson, 1978; Whitty *et al.*, 1977).

4.3.2.1. *Pick's disease*

The illness most closely related to Alzheimer's disease both neuroanatomically and neuropsychologically is Pick's disease, characterized by marked cortical atrophy, frequently of the temporal and frontal regions and resultant dementia (Ball, 1979; Berlin, 1949; Braak *et al.*, 1983; Brun and Gustafson, 1978; Pick, 1892, 1901, 1906; Sjögren *et al.*, 1952; Smith and Lantos, 1983; Terry, 1976). Both diseases belong to the so-called "untreatable dementias" (Strub and Black, 1982), although the onset of the symptomatology differs between the two, with Alzheimer's disease being characterized primarily by cognitive changes and Pick's by changes in personality, social behavior and emotionality (Brun and Gustafson, 1978; Joynt and Shoulson, 1985; Scheid, 1983; Strub and Black, 1982).

Typical descriptions of the progressive course and symptomatology in Pick's disease can be found in Groen and Endtz (1982), Malamud and Boyd (1940), Marin *et al.* (1983), Schenk (1959b) and in Wechsler *et al.* (1982). A variant of the disease with anterior temporal lobe atrophy, the early onset of a Klüver–Bucy syndrome and late occurrence of amnesia was described by Cummings and Duchen (1981).

4.3.2.2. *Encephalitis*

A large number of infections can cause encephalitis (Spatz, 1934), which is often fatal and characterized by an abrupt onset with fever, a confusional state, convulsions, aphasia and increased intracranial pressure (Benson and Blumer, 1982). While some forms of viral infections may only result in transient mnestic disturbances, herpes simplex encephalitis usually leads to severe and lasting mental disorders (Haase, 1978).

Although it is usually assumed that encephalitis primarily affects the cortex and here the temporal lobe (Foletti *et al.*, 1980; Hierons *et al.*, 1978; Koskiemi *et al.*, 1980) and that amnesic states seen in the post-infectious phase are attributable to a neuronal degeneration in these regions, there are older case descriptions with verified neuropathology in which other regions were affected as well (Conrad and Ule, 1951; Ule, 1951). In 1953 Conrad published the results of a detailed neuropsychological examination from an encephalitic patient for whom, however, no neuropathological data are available. The patient was characterized by what Conrad termed a "Minuten-Gedächtnis" (minute-memory), that is, acquired information faded away without residuals within 30–50 sec following presentation. Furthermore, he was disoriented in time and space. Conrad described his performance on a number of memory tests which indicated the existence of a strong "retroactive inhibition" in the patient's behavior. Additional tests revealed severe deficits in his visual perceptual abilities and especially in the ability to reproduce common knowledge such as the Bible story of Adam and Eve or the dates for the beginning and end of the Second World War. The patient gradually recovered after several weeks.

Retroactive interference, which apparently hindered memory consolidation, was also noted in Cermak's (1976) patient, a 44-year old physicist who was said to have had an IQ above 145 prior to his illness. During hospitalization his Memory Quotient was 50, but after a few months increased to 71, with a full IQ of 112, later leveling off at 133 (IQ) and 90 (MQ). At this time he was still unable to remember day-to-day events and had considerable retrograde amnesia. A pneumoencephalogram indicated dilation of the lateral

and third ventricles, marked atrophy of the left temporal lobe, but only some in the right, as well as possible atrophy within the thalamus. On several tasks concerning, for example, rapid information processing, he was superior to Korsakoff patients, while for other tasks his performance was comparable. A more recent evaluation of the patient's memory abilities (Cermak and O'Connor, 1983) confirmed the previous data, suggesting that both the anterograde and retrograde memory defects persisted, but that the patient had developed a strategy for giving answers to questions by generalizing from his semantic memory so as to reconstruct "probable" events.

Other descriptions of the mnemonic information processing abilities of patients with encephalitis similarly stress their prolonged inability to acquire (or to retrieve) new information long-term, while remote memory may be preserved; classical conditionability and memory for motor tasks may also be preserved (Barbizet *et al.*, 1978; Foletti *et al.*, 1980; Gianutsos, 1981; Hall, 1963; Starr and Phillips, 1970; Weiskrantz and Warrington, 1979). Nevertheless, the severity of behavioral consequences of encephalitis may vary considerably between cases. In some cases behavioral disturbances resembling the Klüver–Bucy syndrome may remain (Greenwood *et al.*, 1983), while in others a good recovery may occur even without specific antiviral chemotherapy (Klapper *et al.*, 1984), or only highly specific cognitive defects may remain (Warrington and Shallice, 1984; cf. Section 5.2).

Damasio and Geschwind (1985) recently proposed that the limbic cortices have a special affinity to the herpes simplex type 1 virus. They assumed that the virus is initially transported in a retrograde direction from cutaneous receptors to the trigeminal ganglion and then anterogradely towards the brainstem and the trigeminal nuclei, then to limbic system related nuclei such as the raphe and the locus caeruleus, and from there to almost anywhere else in the cerebral cortex; and especially in the adult it would find proper terrain for multiplying and destroying nervous tissue only in the limbic cortex.

4.3.3. *Other examples of dementic patients*

Patients with a history of hypoxia or ischemia of central nervous system tissue usually show affected brain regions quite similar to those in encephalitic patients and, consequently, the mnemonic changes are closely similar as well (Finklestein and Caronna, 1978; Hirst and Volpe, 1984b; Volpe and Hirst, 1983a).

Chronic alcohol intoxication, on the other hand, may lead to more widespread neuronal tissue changes which affect, among other regions, the whole mass of the cerebral cortex (Cala *et al.*, 1978; Harper and Kril, 1985; Meyer-Wahl and Braun, 1982; Ron *et al.*, 1982). The resultant behavioral deficits, however, seem to be rather variable, with Korsakoff's disease and alcoholic dementia being one extreme.

There are a number of further diseases, such as the Creutzfeldt–Jacob disease (Haase, 1978; Joynt and Shoulson, 1985; Manuelidis, 1985; Roos and Johnson, 1978; Terry, 1976; Tomlinson, 1978), which lead to severe mnestic disturbances, but which are usually coupled to the whole symptomatology of dementia and frequently lead to rapid death, and for these reasons we will not treat them further.

4.3.3.1. *Cases with primarily basal ganglia/extrapyramidal motor system involvement*

Huntington's and Parkinson's diseases are two of several severe illnesses of the central nervous system which ultimately may lead to dementia and which have primarily a subcortical pathology (Butters and Miliotis, 1985; Haase, 1978; Joynt and Shoulson, 1985; Strub and Black, 1982; Terry, 1976; Tomlinson, 1978).

Huntington's disease has a clear genetic cause and leads to neuronal loss especially in the caudate nucleus (Bruyn *et al.*, 1979; Forno and Norville, 1979). Apathy, motor disturbances and mood disorders are seen early, whereas memory functions are affected only later. The progression of the illness is slow. Ultimately, however, the symptomatology may become similar to that of Alzheimer patients but usually without the language disturbances seen in the late stages of Alzheimer's disease (Brandt *et al.*, 1984; Joynt and

Shoulson, 1985; Paulson, 1979). The onset occurs most frequently between the ages of 45 and 55 (Strub and Black, 1982).

Parkinson's disease is a relatively common neurological disorder, characterized by a slowly developing rigidity, tremor, slowness of movement, difficulty in maintaining balance and spatial disturbances (Bowen *et al.*, 1972, 1976; Hoehn and Yahr, 1967; Lieberman, 1974; Sharpe *et al.*, 1983; Strub and Black, 1982). Dementia may only be mild and correlates in degree with the severity of other Parkinsonian features (Mayeux *et al.*, 1983; Strub and Black, 1982). Part of the cognitive defects may be attributable to reduced activity and arousal levels (Hakim and Mathieson, 1978; Lieberman *et al.*, 1979). Morphologically, the substantia nigra is primarily affected (Joynt and Shoulson, 1985).

The subcortical dementia seen in Huntington's and Parkinson's disease has been distinguished from that of the Alzheimer type (Benson, 1984; Cummings and Benson, 1984; Mayeux *et al.*, 1983), and Benson (1983) can be consulted for details of the clinical picture. Pirozzolo *et al.* (1982) gave an extensive set of neuropsychological measures to 60 Parkinson's disease patients and age-, sex- and education-matched control subjects. They found that Parkinson patients exhibited a significantly or highly significantly poorer performance on 21 of their 24 employed measures (cf. their Table 1). 93% of their patients were cognitively impaired compared to controls, although there was a wide inter-individual variance in the degree of the deficits.

That there may well be a substantial variability in cognitive performance and that drug treatment may affect the course of the illness importantly was suggested by a recent study in which Parkinson patients showed normal performance scores on four tests of visual recognition memory, both with and without delay conditions (Flowers *et al.*, 1984).

That demented patients with Huntington's chorea manifest differences in mnemonic information processing when compared with Korsakoff patients was shown in several studies of Butters and co-workers (Albert *et al.*, 1981; Butters *et al.*, 1976, 1978, 1983; Martone *et al.*, 1984; Meudell *et al.*, 1978), two of which will be summarized here. In the study of Albert *et al.* (1981) Korsakoff's and Huntington's disease patients and control subjects were given three tests of remote memory, a facial identification task (including 80 photographs of famous persons from the 1960s to the 1970s), a recall test (with 132 questions on public events and famous people from 1920 to 1975) and a recognition test (multiple choice questionnaire on persons and events prominent between 1920 and 1975).

Both patient groups were severely impaired in all three tests compared to the control group, but between these two groups marked differences could be seen. The Huntington's disease patients had as much difficulty in identifying faces and events from the 1930s and 1940s as those from the 1960s and 1970s, that is, they manifested a *flat* response curve over the decades. The Korsakoff's on the other hand retrieved facts from the distant past more accurately than those from the recent past so that their response curves had a *steep* gradient.

The authors concluded that the flat remote memory curve of demented persons, as compared to that of amnesic patients, argues for a defect in brain regions storing new and old information.

A further differentiation between amnesic (Korsakoff) and demented (Huntington) patients was achieved by giving them tests of skill learning (mirror reading) and verbal recognition (Martone *et al.*, 1984). Korsakoff patients acquired the mirror reading skill at a normal rate but were severely impaired with respect to the recognition of the words used in the task, while Huntington's disease patients were retarded in acquiring the skill, but showed normal verbal recognition.

The results of these and related studies comparing the mnemonic performance of subjects with different, but (probably) restricted brain damage have reinforced the distinction between several forms of memory which may be related to different brain regions, one being more and the other less cognitive in function (or more and less flexible) (Mishkin *et al.*, 1984). Mishkin *et al.* gave the label "memory" to the more cognitive function and related it to a cortico–limbic–thalamic circuit, and termed the other one "habit" and associated it with cortico–striatal structures. As a further distinction and

characterization they considered the memory system as a rapid-learning system, which makes use of single experiences, and the habit system as a slow-learning one which needs repetition.

However, as the authors acknowledged, this distinction may only hold for the information processing of animals, but not for humans with medial temporal lobe or diencephalic damage, as repetitions of an experience apparently do not help the human subjects with such damage in acquiring episodic information long-term (or at most only exceptionally; cf. Section 4.1.2; Kaushall *et al.*, 1981; Zola-Morgan and Öberg, 1980). In spite of the difficulties inherent in such distinctions, they again highlight the probability that the brain is composed of sets of neuronal structures which are involved in long-term information processing but which do so on differing bases of operation (cf. also Markowitsch, 1985a; Pandya and Yeterian, 1984).

4.3.4. *Dementia and amnesia*

As most of the examples given in Section 4.3 show, cases of severe memory disturbances are numerous, but many of them include other cognitive defects which in part overshadow or outweigh the mnestic deficits. Cases with circumscribed traumatic brain lesions show little deterioration in their cognitive behavior and personality over time and even patients with an alcoholic Korsakoff's syndrome may be rather stable over time in their (reduced) cognitive abilities, while cases with an illness leading to dementia may manifest a rather fast deterioration in a number of personality traits including higher intellectual functions, for cases with a Creutzfeldt–Jacob disease, for instance, "the illness runs a rapid and fatal course terminating within 3–9 months of the onset in most classic cases" (Pearce, 1984b, p. 27; cf. also Roos and Johnson, 1978 and Tomlinson, 1978). As the progressive nature will affect brain and behavior of the patient concomitantly, determining "crucial" lesions for the mnemonic domain is difficult.

Concerning the cases with Alzheimer's or Pick's disease, and other degenerative illnesses which affect primarily cortico–limbic regions, they usually have widespread lesions which affect more diverse areas of intellectual functioning, but the similarity to cases with circumscribed medial diencephalic or medial temporal lobe damage is still apparent for the mnestic sphere.

Interestingly, recent work on cases with damage centered primarily in the basal ganglia has resulted in new insights into the functions of these structures, which in traditional neurology had been regarded principally as higher motor centers, and has led to further distinctions between forms of long-term mnemonic information processing. The results furthermore reinforce the view that information storage and retrieval are dependant on a number of networks within the brain with partly distinct, but partly overlapping functions.

Finally, literature on cases with vascular damage of the basal forebrain points to a further regional complex in the brain which is sensitive to long-term memory.

5. Material-Specific Memory Failures

Disorders of specific aspects of short- and long-term memory have been reported to follow lesions of a number of especially cortical foci (De Renzi, 1982; Luria, 1980; cf. also Chapman and Wolff, 1959). In many instances, however, the possible mechanisms underlying the defect are difficult to ascertain, even if pure perceptual or motor disorders can be excluded as complicating factors. Hecaen and Albert (1978), for instance, provided examples of memory disorders associated with frontal lobe and callosal lesions which were at least in part attributable to the usual concomitants of frontal lobe pathology, namely perseveration, lack of initiative and spontaneity or a defective sensory–motor integration. In 1923 Feuchtwanger, too, already considered these last symptoms to be the primary ones after frontal lobe damage, and memory deficits as secondary. Nevertheless, there are some examples of memory-related changes following frontal lobe damage.

5.1. FRONTAL LOBE DAMAGE

In discussing memory changes following different kinds of frontal lobe damage, Damasio (1985b) referred to the ventro–medial pre-frontal cortex as an area in which damage may cause an amnesic syndrome (probably when substantial portions of the basal forebrain regions are affected as well; cf. Section 4.3.1.1), and Pfeifer (1910) also reported that several of his patients with frontal lobe damage had a Korsakoff-like symptomatology.

A short-term memory disturbance had long been attributed to frontal lobe damage and though subsequent studies refuted this, results of recent single unit recordings in animals again indicate that the frontal lobes may participate substantially in short-term information processing (e.g. Fuster and Alexander, 1971; Markowitsch and Pritzel, 1978; cf. Markowitsch, 1986 for review), and Lewinsohn *et al.* (1972) found that patients with frontal lobe damage did more poorly on both visual and auditory short-term memory tasks than did patients with posterior cortical damage.

Risse and co-workers (1984) observed severe impairments in the acquisition and long-term retention of a verbal list learning task in patients with inferior frontal lobe damage and Wallesch *et al.* (1983) found deficits in paired associate learning, digit span, sequential concept formation and in the Benton test in patients with deeper frontomedial lesions.

Finally, Jetter *et al.* (1986) tested retention performance for learned words in a group of 14 patients with postrolandic damage (22 patients had a contusio cerebri, 4 an open skull trauma and 2 infarcts). The patients learned three lists of words each of which had to be reproduced after 15 min and after one day, one list under free recall, one under cued recall and one under a recognition condition. The frontal patients were significantly inferior for the one day free recall condition (Fig. 20). While this deficit can in part be attributed to a reduced attention level or a lack of initiative, drive and concentration, the unimpaired performance under the other conditions, in particular the 15 min free recall, suggests that the patients with frontal lobe pathology indeed showed a deficit with respect to verbal long-term memory. Although this defect was found to exist in subjects with either left or right frontal damage, it was more severe in left-damaged patients.

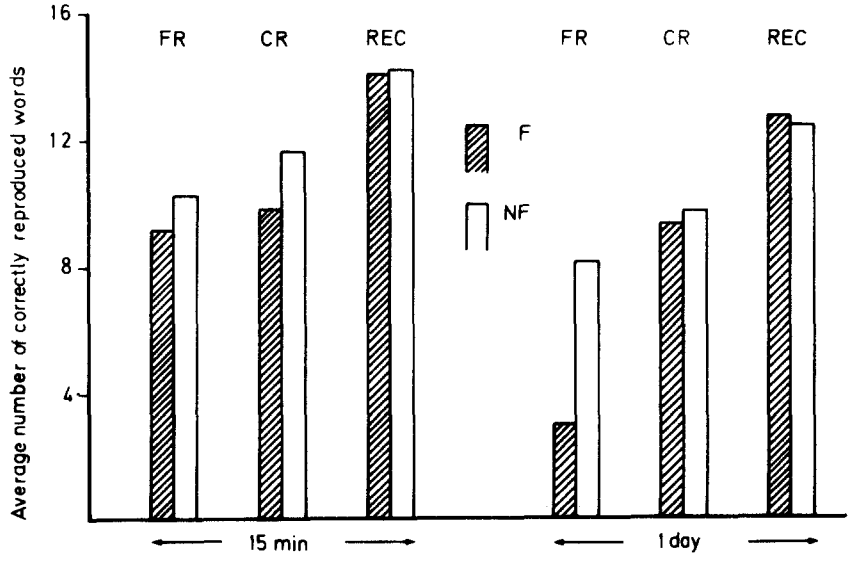

FIG. 20. Memory performance of patients with uni- or bilateral damage to the pre-frontal cortex (group F) or to nonfrontal cortical regions (group NF) during free recall (FR), cued recall (CR) and recognition (REC) of word lists after 15 min and after one day. Note the particularly poor performance of group F during free recall after one day, but not after 15 min. (After data from Jetter *et al.* (1986).)

5.2. OTHER NEOCORTICAL DAMAGE

In 1982 De Renzi summarized memory disorders following focal neocortical damage, reviewing among the material-specific memory defects "face amnesia" or "prosopagnosia". Patients with this selective defect are unable to recognize persons whom they should know well, by face, and have difficulties in identifying some other kinds of visual stimuli. (However, on the basis of galvanic skin response recordings, they do show some evidence of recognition for well-known faces: Tranel and Damasio (1985.))

The illness is rather rare and the lesion necessary to produce it has not yet been strictly determined (cf., e.g. Bodamer, 1947; Damasio *et al.*, 1982; Meadows, 1974). It seems, however, that the lesion, which is usually in the area of the medial occipitotemporal cortex, has to be bilateral, or at least involves callosal fibers, in order to be distinctly present (Damasio, 1985a). The stimuli which these patients are unable to identify depend on contextual (episodic) memory, on a personal, spatially and temporally bound memory process, and for this reason Damasio (1985a) considered the defect "as a disorder of visually-triggered contextual memory" (p. 134).

As a further material-specific memory defect, De Renzi listed "color amnesia" which can be seen in a variety of test situations, for example in aphasics under nonverbal testing conditions (Cohen and Kelter, 1979; Damasio and Damasio, 1983; De Renzi *et al.*, 1972; Geschwind and Fusillo, 1966; Varney and Digre, 1983). In the case of Varney and Digre (1983) the lesion was assumed to be in the left parietal area, possibly affecting the superior temporal area as well. The patient, a 63-year old man, was given a number of tests on color identification, including the Ishihara Test of Color Blindness, in which multi-color-stippled numbers have to be identified against a multi-color-stippled background, and here he made no errors on a 32 item version, while on tests of color naming or color association learning he was grossly defective. There was some recovery from the deficit after six months.

While this patient was also impaired in identifying colors after learning the names, Davidoff and Ostergaard (1984) recently described a patient who was able to point to the colors someone called for, but still had a marked color anomia without object anomia. The authors interpreted his impairment as a short-term memory deficit specific to color. The patient had a well-localized infarct in the left occipito–temporal region (presumably from an occlusion of the left posterior cerebral artery). His verbal IQ was 108, his performance IQ 86.

Ross (1980a) described a patient with combined color anomia and prosopagnosia (see below).

As a third category of material-specific defects, De Renzi (1982) discussed "topographical amnesia", the inability to remember the location of an object in the environment and its spatial relations to other objects. This deficit is coupled to posterior parietal lobe damage, or the temporo–parieto–occipital junction area (though De Renzi listed two case reports in which the damage was confined to the medial occipital lobe).

Selective anterograde amnesia for the visual or for the tactile modality was described by Ross (1980a,b). Ross (1980a) observed an isolated loss of visual recent memory in two cases with tasks in which they had to reidentify relatively nonverbalizable objects following a three min verbal distraction time. Both patients had bilateral infarcts in the medial occipital lobes as evaluated by CT-scanning. Ross proposed the existence of a bilateral disconnection syndrome between the striate cortex and the medial temporal lobe structures as responsible for the deficit, writing "...the lesions served to prevent visual information from gaining access to the inferotemporal cortices, which in turn connect via the entorhinal cortices to the neuronal structures in the medial temporal lobes that are known to be imperative for recent memory function..." (p. 199; cf. also his Fig. 8 which is a schematic illustration of the route from the visual as well as for the auditory and somatosensory modalities).

In addition, Ross (1980b) found three cases with unilateral tactile loss of recent memory. In two patients the loss occurred in the right hand and was accompanied by verbal anterograde amnesia, in the third case, the left hand was affected without any additional

kind of amnesic disorder. The lesion locus was assumed to be in the medial temporal lobe contralateral to the affected hand.

Another kind of memory disconnection syndrome with parallels to prosopagnosia is the so-called reduplicative paramnesia, already described by Pick (1903), in which the primary symptom is the duplication of persons (including oneself), places, time and events (Patterson and Mack, 1985; Ruff and Volpe, 1981; Staton *et al.*, 1982). Staton *et al.* held an impaired ability to integrate newly acquired information with older memories as the cause of the symptoms. The lesions causing this disturbance may be quite different as to the locus. In the four cases of Ruff and Volpe (1981) they were found in the right frontal and/or parietal lobe, whereas in the case of Staton *et al.* (1982) the region of the right posterior hippocampus and adjacent temporal lobe as well as regions of the temporo–parietal junction were affected, but mild atrophy was also seen in the right parieto–occipital junction and in frontal lobe regions. With respect to mnestic functions, the most significant deficits in the case of Staton *et al.* were in short-term visual memory and in the reproduction of designs.

Specific short-term memory defects following neocortical lesions were also described in several reports from Warrington and co-workers (Shallice and Warrington, 1977; Warrington *et al.*, 1971; Warrington and Shallice, 1969). The results given in these reports have been considered as further evidence for a distinction between short- and long-term memory with a morphological substrate for short-term memory being in the area of the supramarginal and angular gyri of the left hemisphere (cf. also Saffran and Marin, 1975). Their first reported case, called K.F., had received a left parieto–occipital fracture in a motor-bicycle accident at the age of 17 years and at 19 he had become epileptic. He was tested neuropsychologically at an age of 28 years, his verbal IQ being 79 and his performance IQ 113. His memory for day-to-day events was good and he had an adequate knowledge of recent and past events, but the most striking feature in his behavior was an almost total inability to repeat verbal stimuli: his digit span covered only two items, and this even decreased when repeated attempts were made. As with digits, he had difficulties in repeating letters, disconnected words and sentences.

In a number of tests, Warrington and Shallice (1969) demonstrated the inability of K.F. to hold within his short-term store any sequences of items beyond a certain length (reinforcement, however, occasionally improved his performance). On the other hand, in tests of long-term memory such as paired associate learning, K.F. was almost at the level of normal subjects of his age. For instance, he could recall 9 out of 10 associations after a delay of 6 hr. Similarly, on the Gollin's incomplete pictures test, he performed in the normal range.

K.F.'s basic defect therefore lay in his reduced repetition ability, that is, in an impaired short-term memory (in particular for the auditory modality), while the long-term memory, on the other hand, was normal, especially considering his IQ. Two further cases with a rather similar symptomatology were described two years later by Warrington and co-workers (1971). One of the patients had a meningioma in the left posterior temporo–parietal zone which was removed; the other had a behavioral symptomatology suggesting brain damage and showed a moderate dilation of the whole left lateral ventricle, but no definite damaged brain region was determined. Finally, a fourth case, with principally the same auditory short-term memory defect and a lesion in the left posterior parietal cortex, was thereafter presented by Saffran and Marin (1975).

In 1977 Shallice and Warrington discussed theoretical implications of this deficit and compared the hypotheses of others with their position, which explained the symptomatology in terms of an auditory–verbal short-term memory deficit.

As a last case in point with neocortical damage and specific mnestic defects, Warrington and Shallice (1984) described a surprisingly selective mnemonic deficit in four patients (two males, aged 23 and 48, and two females, aged 44 and 60) who had partially recovered from herpes simplex encephalitis. All four were able to identify inanimate objects but were severely impaired in identifying living things and foods when tested months or even years after the onset of the illness.

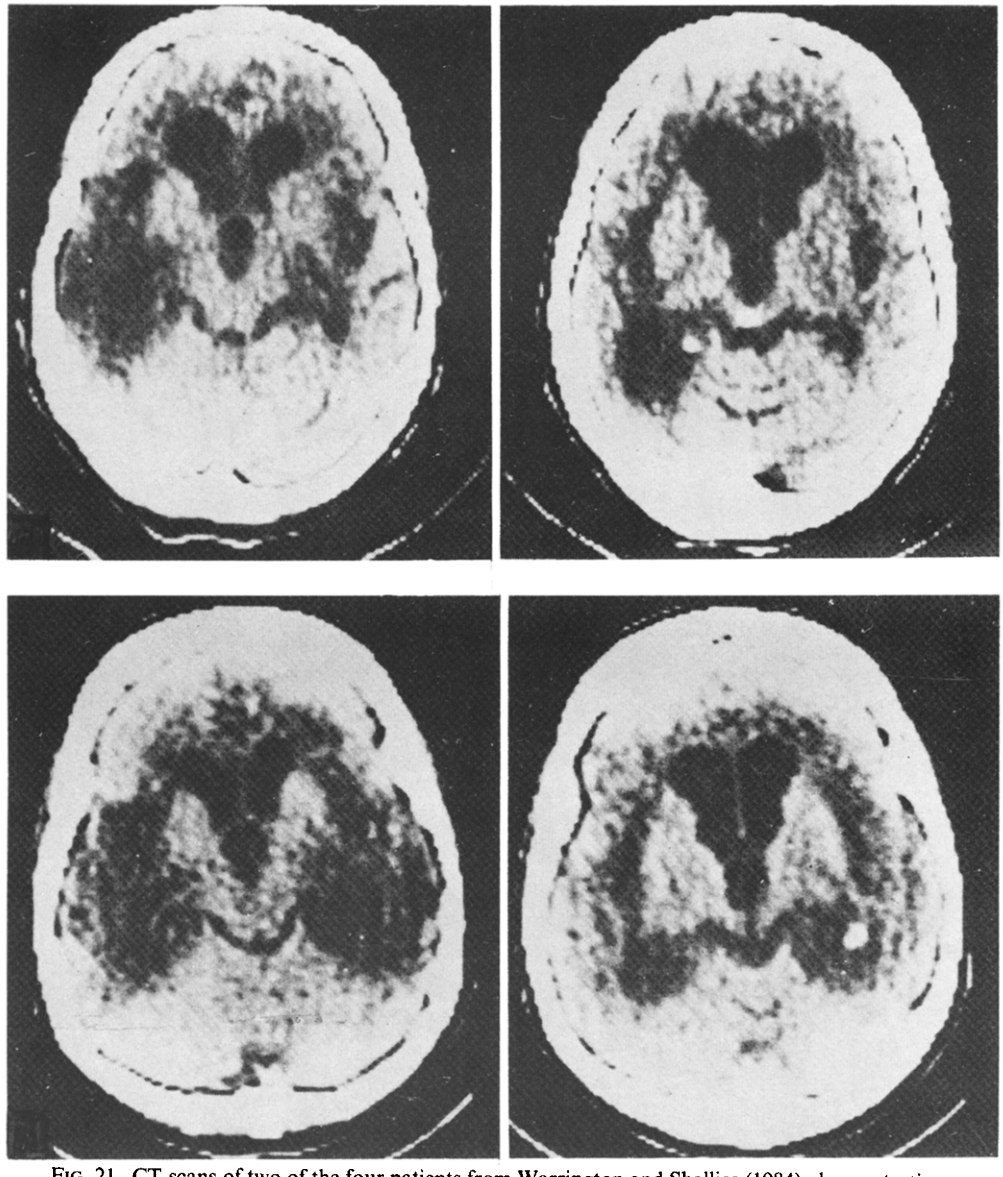

FIG. 21. CT-scans of two of the four patients from Warrington and Shallice (1984), demonstrating predominantly bitemporal damage. The upper pictures are from one patient, and the lower from another. (From Warrington and Shallice (1984), reproduced with permission.)

The deficit was most clearly apparent when a set of 96 colored pictures (with 48 animals or plants and 48 inanimate objects) was presented to those two patients who could express themselves rather lucidly and fluently. While the two sets did not differ significantly in their demands on word fluency, the subjects were able to give accurate definitions or descriptions of terms such as tent, briefcase, compass, submarine, umbrella, but not for living things such as wasp, parrot, snail, eel or spider. Nevertheless, they were usually able to identify the superordinate category when the objects were presented orally. One of the patients furthermore was found to be very poor in his comprehension of food names, though again he performed quite well in identifying the superordinate.

All four patients showed low attenuation bilaterally in the temporal lobes. Figure 21 gives an example of the CT-scans for two patients.

6. Retrograde Amnesia

When amnesia is mentioned, it more often means anterograde amnesia, as cases of memory disturbances without anterograde amnesia are extremely rare. Hirst (1982) and Levin *et al.* (1982), for instance, referred to Russell and Nathan's (1946) report in which 1,029 head trauma patients were surveyed and in which retrograde amnesia was always accompanied by anterograde amnesia, and a similar observation was made by Teuber (1968). In fact, there is only one single case description of a patient with a severe and persisting retrograde amnesia (for the previous 40 yr) *without* evidence for an anterograde memory deficit (Andrews *et al.*, 1982).

Because it is interesting from both a psychological and a neurological point of view to investigate the reasons why rather different brain lesions may lead to a lasting recent memory deficit, but usually only to a limited deficit in old memory, some of the data on possible relations between retrograde amnesia and circumscribed brain damage will be summarized here separately so as to complement the recent survey of Parkin (1984, pp. 485–489).

A few studies can be briefly mentioned which discussed retrograde amnesia in the context of certain possibly related phenomena. Apart from a rather old survey (Paul, 1899), Williams (1969) gave a description of relations between retrograde amnesia and normal forgetting, and Benson and Geschwind (1967) distinguished between retrograde amnesia, supposedly caused by a deficit in initial encoding or storage of information, and retrograde amnesia, assumed to be caused by a deficit in the retrieval of information. According to these authors, the first form is found in cases with an intact ability to learn new information, the second form in cases with an enduring impairment in recent memory. This distinction, however, has to be questioned in the light of the case with pure retrograde amnesia without concomitant anterograde amnesia mentioned above (Andrews *et al.*, 1982). Whitty and Zangwill (1977) emphasized the usually short period of retrograde amnesia which frequently only has a time span of minutes or hours, rather than days, months or years.

Finally, Crovitz *et al.* (1983) tested 1,000 young adults with a retrospective self-report questionnaire "designed to (1) sample the frequency of all head injuries with loss of consciousness in a given population, and (2) quantitatively access the inter-relationships among post-taumatic amnesia (...), retrograde amnesia (...), and time since injury" (p. 407). They found that the severity of anterograde and retrograde amnesia and time that had passed since the head injury were related to each other.

6.1. Traumatic Amnesia

Sudden external force most likely leads to retrograde amnesia, though usually for only a short duration (e.g. Russell, 1971; Russell and Nathan, 1946). Amnesia of this kind is frequently brought on by contusions suffered in traffic (Russell, 1935, 1971), household accidents (Fisher, 1966), or during football matches (Yarnell and Lynch, 1970, 1973), boxing (Blonstein and Clarke, 1957; Critchley, 1957; Grahmann and Ule, 1957) or following penetrating missile wounds of the brain (Teuber, 1968).

Frequently for these cases with traumatic brain damage, there is no (or at best only a slight) indication of the underlying changes in the brain. Symonds (1962), for instance, considered temporal lobe damage (traumatic or otherwise) as leading to retrograde amnesia, a suggestion which has not received unequivocal support from the results of other kinds of cases. The data of Warrington and Shallice (summarized in Section 5.2) on patients with temporal lobe damage and a selective defect in identifying living things and foods might be interpreted as a retrograde amnesic defect; similarly, Dimsdale and co-workers (1964) described a patient in whom a right temporal lobectomy resulted in retrograde amnesia for 10 years prior to operation, and the results obtained by stimulating the temporal lobes electrically (cf. Section 4.1.6) are in favor of a role of this region in information retrieval. On the other hand, the absence of a long duration retrograde amnesia in patient H.M. (cf. Section 4.1.2) clearly contradicts the suggestion. However, there is only a limited similarity in the temporal lobe damage of the cases mentioned above so that it is likely that specific regions within the temporal lobes are involved in the retrieval of pre-morbid information and in the encoding and/or retrieval of information gained afterwards.

A further likely possibility is that temporal lobe damage leads to profound retrograde amnesia in interaction with damage to other brain structures; that this might be the case is suggested by the recent case descriptions given by Damasio *et al.* (1985a,b), Goldberg *et al.* (1981, 1982), Roman-Campos *et al.* (1980) and by Rousseaux *et al.* (1984) (although the cases given by Damasio *et al.* and Roman-Campos *et al.* had brain damage of nontraumatic origin).

6.1.1. *Case of Goldberg* et al. (*1981, 1982*)

The case of Goldberg *et al.* (1981, 1982) is of special interest with respect to the involvement of brain structures involved in the processing of stored memories, as the patient recovered from his anterograde memory defect, but not from a severe retrograde amnesia and as there is CT proof of the brain damage. The authors described the 36-year old college-educated man as having "an open skull fracture in the right parieto–occipital and temporal areas and herniation of the right hemisphere with compression of the left mesencephalon at the tentorial notch" (p. 1392). Following surgery (with removal of a small portion of macerated brain tissue) a series of CT-scans was performed which revealed "moderate ventricular enlargement, a region of rarefaction in the right middle and posterior temporal areas, and a small region of rarefaction along the left midtemporal convexity" (p. 1393). Furthermore, "a narrow band of hypodensity in the median and left paramedian zones, extending from the ventral tegmental portion of the upper mesencephalon (...) caudally to the ventral portion of the ponto–mesencephalic junction" (p. 1393) was found to exist (cf. Fig. 1 of Goldberg *et al.*, 1981). Also, tissue density was altered in the region of the ventral tegmental nucleus, that is, in an area in which a component of the medial forebrain bundle originates, and in another area of efferents from the locus caeruleus.

Initially, the patient had both a severe anterograde and a severe retrograde amnesia, but the anterograde amnesic state improved considerably during the two year course of recovery reported on. The retrograde amnesia, on the other hand, persisted in his answers on questions for general information (such as the capitals of countries or well-known figures from fiction) and on standardized tests. Six weeks following surgery the patient considered himself to be 16 to 18 years of age, gave the address of his parents as his residence and showed no knowledge of his subsequent life history (marriage, children, past employment).

The authors suggest that, in a similar way to the hypothesis of reverberatory activity being crucial for memory consolidation (Hebb, 1949; Vinogradova, 1975; Vinogradova *et al.*, 1976; cf. also Kornhuber, 1973, and Markowitsch, 1985a), memory retrieval might also occur on the basis of reverberation, but dependent on some intrinsic reticular activation. Based on their CT findings, they assumed that a disruption of ascending reticular

projections into limbic structures (hippocampal formation, mamillary bodies) was the principal cause of the retrograde memory deficit, that is, they proposed that selective mesencephalic reticular activation of limbic brain regions constitutes a fundamental component of long-term retrieval.

If this speculation should be confirmed by further cases—and Goldberg *et al.* (1982) found the case described by Roman-Campos *et al.* (1980) to be closely similar in the probable neuropathology—the ventral mesencephalic region might be termed a "bottle-neck" for the transmission of old memories.

6.2. Comparison of Cases with Different Etiologies

Compared to cases with anterograde amnesia as the primary symptom, it is apparently even more difficult to determine the loci of brain damage in cases with extensive retrograde amnesia as the principal disorder. Although several cases have been published which are rather interesting from a psychological standpoint, their neuropathology could be treated only speculatively (e.g. Andrews *et al.*, 1982; Roman-Campos *et al.*, 1980; Schacter *et al.*, 1982). One possible reason for this may be seen in the fact that retrograde amnesia is clinically of rather minor importance compared to anterograde amnesia with respect to the consequences to the individual (Butters, 1984; Teasdale and Brooks, 1985). However, because of the great theoretical interest in how mnemonic events are consolidated and stored in the brain and in the question of whether different kinds of lesions might have an effect on the duration of an amnesia and/or on the kind of material afflicted, the results of some studies dealing with those questions will be discussed here briefly.

6.2.1. *Temporal gradients*

As is apparent from the description of the case from Goldberg *et al.* (see Section 6.1.1), for cases with even a severe and lasting retrograde amnesia this is usually time-limited. Although Goldberg *et al.* provided no details, it appears from the available data that the retrograde amnesia had been rather complete for events of the previous 20 years, but did not affect at all (or only to a much lesser degree) those of his first 16 to 18 years (for instance, he could recall his parents' home address but not his present one). While it is a common occurrence that very remote memories are spared even in cases with extensive retrograde amnesia, the question of whether a more complete amnesia exists for events immediately preceding the head injury, as opposed to those further back in time, became a matter of some controversy and led to the introduction of several methodological approaches (e.g. Crovitz and Schiffman, 1974; Levin *et al.*, 1977, 1985; Marslen-Wilson and Teuber, 1975; Sanders and Warrington, 1971; Squire and Slater, 1975; Zola-Morgan *et al.*, 1983) (cf. Fig. 5).

The study of Sanders and Warrington (1971) was among the first specifically addressed to this question. Five amnesic patients participated: three with an alcoholic Korsakoff syndrome, one with right temporal lobectomy (but without any left-sided pathology) and one who had suffered coal gas poisoning. They received a questionnaire on "famous events" and a test of famous faces. Compared to 200 control subjects who filled out the questionnaire and 100 who performed the famous faces test, the patients were all impaired to an equal degree for the time between 1930 and 1968. (A similar degree of impairment of remote memories irrespective of the time period addressed to was also found for normal subjects by Warrington and Sanders (1971).)

The authors concluded from their data that "no evidence has been found to support the view that remote memories, at least for the time span covered..., are spared or less impaired than memory for recent events" (p. 665), that is, they failed to confirm the so-called Ribot law (Ribot, 1882; cf. Section 2.1).

Two subsequent reports with alcoholic Korsakoff patients as amnesic subjects, however,

did find evidence in favor of Ribot's law (Marslen-Wilson and Teuber, 1975; Seltzer and Benson, 1974). In Seltzer and Benson's study the Korsakoff's were better in remembering famous events from the 1930s and 1940s than from the 1960s and 1970s, while in Marslen-Wilson and Teuber's study they were better at identifying famous faces from the 1960s than from the 1930s and 1940s.

Butters (1984), Butters and Brandt (1985) and Butters and Albert (1982) discussed these and related data. They did not consider Warrington correct, who assumed that the difference between their data and those of others might be related to the relative difficulty of and controversy over the test items; they referred to the results of more recent experiments on this topic (Albert *et al.*, 1979; Cohen and Squire, 1981; Meudell *et al.*, 1980; Squire and Cohen, 1982; Squire and Slater, 1975; but see Mair *et al.*, 1979; Fig. 13).

Albert *et al.* (1979) found a steep temporal gradient in their Korsakoff patients both on the famous faces test and on a recall questionnaire. This gradient was similar for items which were hard to identify (Tiny Tim, Rosemary Clooney) and those which were easy (Charlie Chaplin, Charles Lindbergh) (cf. Figs 2 and 3 of Albert *et al.*, 1979, or Fig. 5 of Butters, 1984).

Cohen and Squire (1981) and Squire and Cohen (1982) gave their remote memory test battery to Korsakoff's disease patients, to depressed patients receiving bilateral electroconvulsive therapy (tested on the day prior to their first treatment in the series and again at least one hr after the fifth treatment), to N.A. (described in Section 4.2.1.5) and to subjects of two control groups (one for N.A. and the other for the Korsakoff patients). Their data revealed a distinction between the degree of remote memory impairments, with the Korsakoff patients having an extensive defect on this variable, while the patients with electroconvulsive therapy and N.A. had only a restricted one. Korsakoff patients manifested a temporal gradient for most of the tests given.

Cohen and Squire (1981) concluded from these observations that the locus and extent of the brain lesions determine the characteristics of the amnesia. That is, the locus primarily determines the kind of amnesia, and the extent of damage determines the amount of pre-morbid time which is lost.

Another variable of importance (which may also help solve the contradictory findings of Sanders and Warrington (1971) and Mair *et al.* (1979) on the one hand, and, on the other, of Butters and co-workers [see also Fig. 5]) appears to be the salience of the items tested; Levin and co-workers (1985) recently found that, during post-traumatic amnesia, salient stimuli such as autobiographical events are memorized with a steep gradient (according to Ribot's law), while for less salient stimuli such as television programs no such gradient existed.

Using the data from Squire and Cohen (1981) and the results obtained together with Albert (Butters and Albert, 1982), Butters (1984) suggested that the temporal gradient in remote memory testing found in Korsakoff amnesics (older events being better preserved than more recent ones) "may be secondary to a primary defect in establishing new memories (anterograde amnesia) during the 20 years of alcohol abuse that preceded the diagnosis of the amnesic syndrome" (p. 234). While there is some controversy on whether detoxified non-Korsakoff alcoholics still show anterograde memory defects or not (cf. Butters, 1984, or Markowitsch *et al.*, 1986), a positive relation at least between years of alcohol abuse and memory deterioration appears established (Brandt *et al.*, 1983; Markowitsch *et al.*, 1986; Ryan and Butters, 1980a,b). Thus, as an explanation of their retrograde amnesia: "...the Korsakoff patients' loss of remote memories would be considered an artifact related to a primary defect in establishing new memories and to a cognitive problem in locating memories that have been successfully stored" (Butters, 1984, p. 234; cf. also Albert *et al.*, 1980).

That this kind of memory loss in retrograde amnesia may be similar to that affecting the acquisition of post-morbid information was recently shown by Squire *et al.* (1984b) who demonstrated the retention of the skill to read mirror-reversed words in patients treated with electroconvulsive therapy. (As stated earlier, it is frequently assumed that brain regions typically affected by electroconvulsive therapy are the temporal lobes.)

6.3. BRAIN LOCI RELATED TO RETROGRADE AMNESIA

These last examples indicate an involvement of either temporal lobe structures (cases receiving electroconvulsive therapy) or diencephalic midline structures (Korsakoff patients) in the processing of old memories. Comparing this latter group of patients with case N.A., Butters and Cermak (1980) speculated "that the alcoholic Korsakoff patients' severe anterograde amnesia develops slowly due to the gradual atrophy of the dorsomedial nucleus, whereas their loss of remote memories appears suddenly with acute damage to other subcortical or cortical brain structures" (p. 169). In 1984, Butters repeated this hypothesis, but omitted the reference to cortical structures, which seems important as other authors consider cortical, in particular frontal lobe, damage as related to memory disturbances (e.g. Moscovitch, 1982).

Because patients with encephalitis frequently have a severe retrograde amnesia and cortical damage in the temporal lobe and possibly elsewhere, they can be considered as a further group of brain damaged subjects (e.g. Cermak, 1976; Cermak and O'Connor, 1983), as well as the cases of Roman-Campos *et al.* (1980), Damasio *et al.* (1985a,b), Fedio and Van Buren (1974) and those of Alexander and Freedman (1984) and Gade (1982) with basal forebrain damage.

Damasio *et al.* (1985a) described a 55-year old man, who had a prominent amnesic syndrome following extensive bilateral damage to the temporal lobe and basal forebrain, caused by herpes simplex encephalitis. CT-scanning revealed that this damage included bilaterally most of the orbitofrontal cortex and all of the basal forebrain gray matter. The anterior cingulate gyrus and the medial temporal lobes including the hippocampus and amygdala were involved bilaterally as well. The patient had a retrograde amnesia which spanned 50 years and spared only semantic material and some few previous experiences which lacked appropriate temporal or spatial placement. Damasio *et al.* (1985a) supposed that the lesions of the lateral temporal lobes and the insula (with or without those of the basal forebrain) were responsible for the patient's grossly defective retrograde memory.

The conclusion that "an assessment of what individual structures are contributing to a patient's amnesic symptoms becomes nearly impossible" (Butters and Miliotis, 1985, p. 414) is justified when one compares the above-mentioned cases with that of Goldberg *et al.* (1981), in which midbrain damage was considered to account for the retrograde amnesia, and with dementia patients suffering from Huntington's disease, who had a flat, low-level retrograde memory curve (cf. Butters and Albert, 1982) and who were assumed to have primarily basal ganglia damage (see Section 4.3.3.1). While the conclusion may hold in spite of the limited knowledge on anatomico–behavioral relations with respect to retrograde amnesia, we will nevertheless point to the differentiation between three forms of retrograde memory deficits given by Albert (1984b). The first form is exemplified by the cases with electroconvulsive therapy (Cohen and Squire, 1981; Squire *et al.*, 1975) or with head trauma patients (Russell, 1971). These cases have limited retrograde amnesia which recovers to a considerable degree over time. The second group is exemplified by cases with Korsakoff's disease in which the retrograde amnesia covers several decades and usually shows a temporal gradient and the third group is constituted by patients with advanced Huntington's disease and probably by senile dementics (Wilson *et al.*, 1983), with a retrograde amnesia for several decades, but no temporal gradient (indicating equivalent losses in remote memory for all periods of their lives).

7. Animal Models of Global Amnesia

While the registration of memory disturbances following experimental brain lesions in animals dates back to the last century (e.g. Brown and Schäfer, 1888; Ferrier, 1875, 1886; Ferrier and Yeo, 1884) and was in fact the subject of pioneering work in physiological psychology (e.g. Lashley, 1929, 1950), a systematic search for animal models comparable in brain pathology to human subjects with amnesia was not begun until relatively late and prompted special attention after the reports of cases such as H.M. (e.g. Drachman and

Ommaya, 1964; Orbach *et al.*, 1960; Weiskrantz, 1964). The outcome of these studies usually failed to reveal close similarities to the human amnesic syndrome, a discrepancy which was attributed partly to differences in the tasks used to study memory in animals (especially monkeys) and partly to inter-species differences between human and nonhuman primates (see, e.g. Iversen, 1973, 1976, 1983; Weiskrantz, 1964, 1978, 1982a,b). From his comparison of studies on memory disturbances in animals and man, Weiskrantz (1982b) concluded that the "...difficulty is that we still do not know whether any of these deficits [found in animals] is, indeed, functionally homologous to the human amnesic deficit. It is even quite possible—we would say likely—that a more severe learning or retention deficit in animals will emerge from lesions that are quite irrelevant to the amnesic deficit than from other lesions that ultimately turn out to be directly relevant" (p. 301).

A different, more optimistic view is held by Mishkin and co-workers (Mishkin, 1982; Mishkin *et al.*, 1982) and by Squire and Zola-Morgan (Squire and Zola-Morgan, 1983; Zola-Morgan, 1984). These authors based their view on a number of recent experiments in which complex learning tasks (some only recently developed) had been given to animals with different lesions of medial temporal lobe or of diencephalic structures. We will give a short survey of some of these reports in the following.

7.1. Models of Diencephalic Amnesia

Diencephalic lesions in animals can be found following chronic alcohol intoxication (Irle and Markowitsch, 1983b), or following thiamine deficiency (evoked in order to induce Korsakoff's disease-like consequences) (Irle and Markowitsch, 1982c; Witt and Goldman-Rakic, 1983a,b) or specific lesions are made in order to test the function of thalamic nuclei or the mamillary bodies in the processing of mnemonic information (Aggleton and Mishkin, 1983a,b; Chow, 1954; Irle and Marlowitsch, 1982d, 1983a; Isseroff *et al.*, 1982; Markowitsch, 1982a,b).

The results of these studies were quite disparate with respect to the behavioral alterations observed (cf. Table 1 in Markowitsch, 1982a). Chow (1954) found normal retention of discrimination and spatial delayed response tasks in monkeys with lesions of the mediodorsal and pulvinar nuclei. In the studies on cats significant deficits in the acquisition (Irle and Markowitsch, 1982b,c, 1983a) or retention (Markowitsch, 1982b) of delayed alternation-type tasks were found; however, most of the animals were able to acquire or reacquire the tasks, although the lesions of the mediodorsal nucleus were sometimes complete and selective (Fig. 22). Lesions of either the mediodorsal nucleus or the mamillary nuclei alone, or the mediodorsal nucleus in combination with the mamillary bodies had similar effects (Irle and Markowitsch, 1982c).

Similarly, Isseroff *et al.* (1982) found a significant impairment in a spatial alternation and a spatial delayed response task in monkeys with mediodorsal lesions (Fig. 23), but not in tests on object reversal or visual pattern discrimination (Figs 24 and 25). Nevertheless, in this study, too, nearly all of the animals finally reached criterion in the alternation tasks, and in the studies of Aggleton and Mishkin (1983a,b) as well, monkeys with mediodorsal nucleus lesions were impaired, but most of them were still able to reach criterion in the learning tasks employed.

In our view, the amnesic syndrome, as seen in patient N.A. with a selective and apparently only unilateral lesion of the mediodorsal nucleus, has not yet been confirmed in animals, at least not with the learning tasks used.

7.2. Models of Medial Temporal Lobe Damage

During the last 10 years several groups of workers have attempted a new direction for an animal model of human medial temporal lobe amnesia. This was done on the one hand by refined testing methods, and on the other hand by using restricted kinds of lesions, such as the fornix (Bachevalier *et al.*, 1985a,b; Carr, 1982; Gaffan, 1974, 1977, 1983; Gaffan and Harrison, 1984; Gaffan *et al.*, 1984a,b,c; Gaffan and Weiskrantz, 1980; Mahut *et al.*,

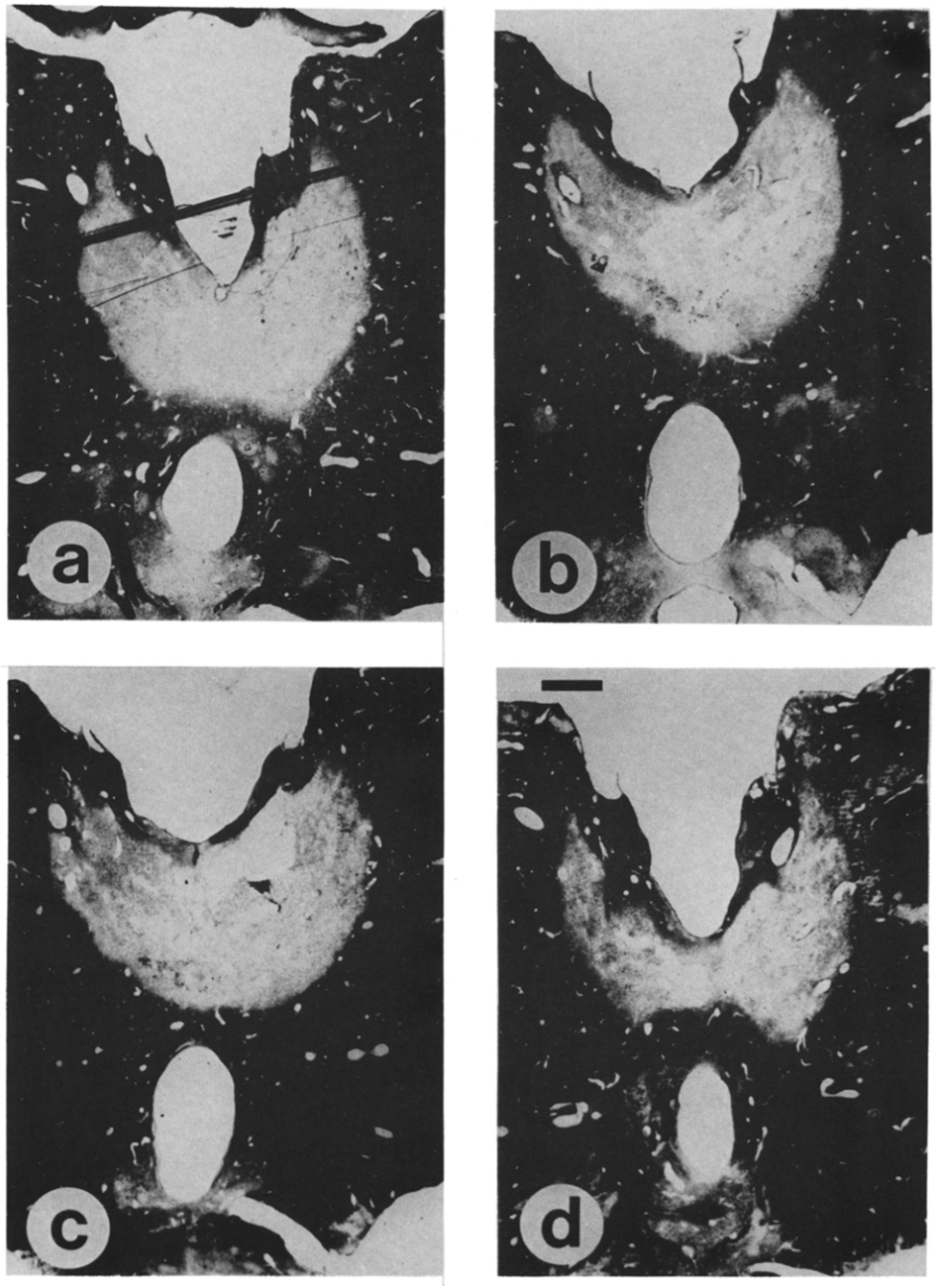

FIG. 22. Coronal sections through the middle portion of the thalamus of a cat brain from anterior (a) to posterior (d). The extent of the kainic acid-destroyed area contrasts sharply with the rest of the thalamus (modified Klüver–Barrera stain), (a) about level 10.0 mm, the diagonal stripes have been caused by a break in the glass of the slide; (b), (c) and (d) these correspond roughly to anterior–posterior levels A 9.0 mm, A 8.5 mm and A 7.5 mm. The scale in (d) is 1 mm and holds also for (a)–(c). (From Fig. 2 of Markowitsch (1982b), reproduced with permission.)

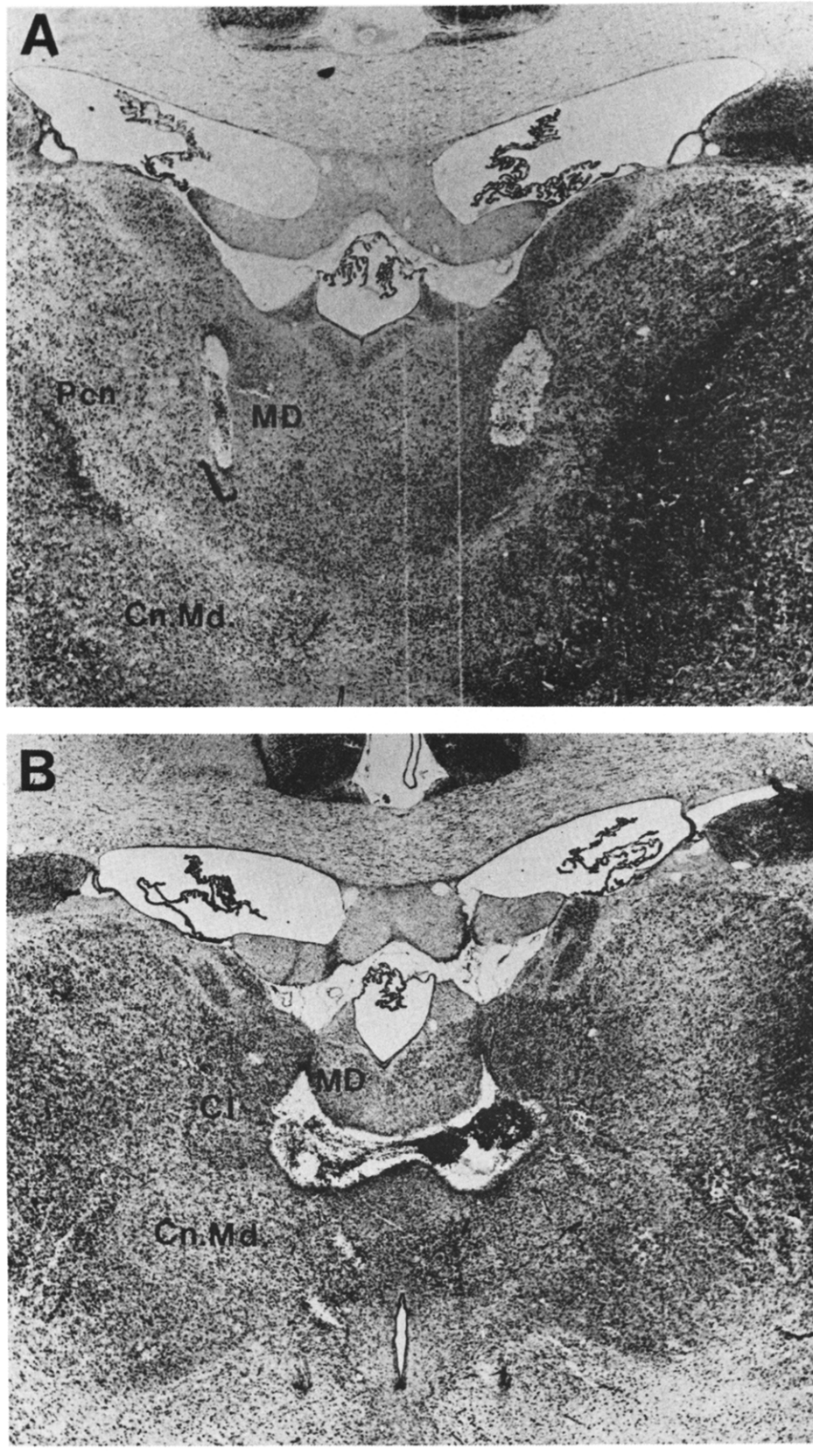

FIG. 23. Photographs of coronal sections through the area of the rhesus monkey medial dorsal thalamus. The extent of a small radiofrequency-produced lesion is shown in (A), that of a large lesion in (B). (From Fig. 2 of Isseroff *et al.* (1982), reproduced with permission.)

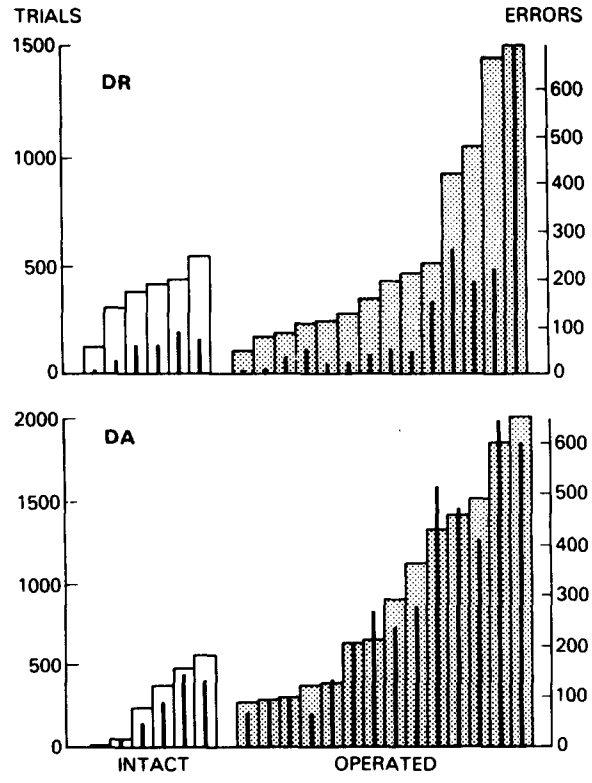

FIG. 24. Performance of individual monkeys (control animals, open bars; animals with lesions of the mediodorsal nucleus, shaded bars) in delayed response (DR) and delayed alternation (DA) tasks. Smaller central stripes give errors to criterion. (From Fig. 4 of Isseroff *et al.* (1982), reproduced with permission.)

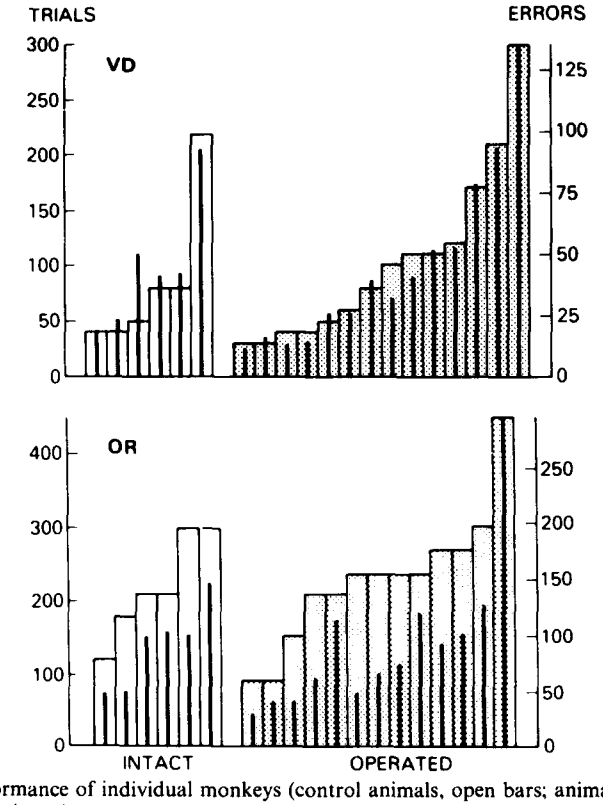

FIG. 25. Performance of individual monkeys (control animals, open bars; animals with lesions of the mediodorsal nucleus, shaded bars) in visual discrimination (VD) and object discrimination reversal (OR) tasks. Smaller central stripes give errors to criterion. (From Fig. 5 of Isseroff *et al.* (1982), reproduced with permission.)

1982; Moss *et al.*, 1981; Owen and Butler, 1982, 1984; Zola and Mahut, 1973; Zola-Morgan and Squire, 1984), the hippocampus together with the amygdala (Mahut *et al.*, 1981a; Malamut *et al.*, 1984; Mishkin, 1978; Murray and Mishkin, 1983, 1984; Saunders *et al.*, 1984; Zola-Morgan and Squire, 1985) or the amygdala alone (Murray and Mishkin, 1985).

7.2.1. *Fornix damage*

While it is still a matter of debate as to whether in humans damage to the basal forebrain usually results in amnesia or not (see Section 4.1.7), the results of fornix lesions in monkeys lead—at least on a general level—to similar kinds of mnemonic alteration as do lesions of medial temporal lobe structures.

The fornix sections performed by Gaffan for instance were intended "to determine the part played by the hippocampus in 2 different kinds of memory: association and recognition" (Gaffan, 1974, p. 1100). With "recognition memory" Gaffan (1974) meant "the ability to judge familiarity, that is, to discriminate familiar from novel items" (p. 1100), and with "association memory" "the memory of what went together with an item" (p. 1100). While Gaffan proposed in several articles that fornix transection impaired recognition but not association memory (e.g. Gaffan, 1974, 1977; Gaffan and Weiskrantz, 1980), and considered this deficit as behaviorally similar to human recognition memory for nonverbal material (Gaffan and Weiskrantz, 1980), more recently he abandoned this view in the light of the results of an experiment in which monkeys with fornix transection were impaired in association memory as well (Gaffan, 1983). The task used in this experiment was called "Win Shift Lose Stay" and required the monkeys during the retention test to choose the object that had been associated previously with nonreward.

Recently, Gaffan and co-workers (Gaffan *et al.*, 1984a,b,c) concluded that the "impairment produced by fornix transection is best seen... as an increase in confusability" and "that the hippocampus keeps track of specific responses in specific contexts, the specification in question being somewhat more detailed and precise than the rest of the brain can manage on its own" (Gaffan *et al.*, 1984b, p. 211). They characterized the deficit produced by fornix transections as an impairment for memory of instrumental responses (Gaffan *et al.*, 1984a,b,c). This proposition may have some validity especially because it is formulated in such a general way that it avoids the problems inherent in taking into account possible differences in the action of specific subregions of the hippocampal complex (Markowitsch, 1985d), it is, furthermore, similar to the conclusion of Gaffan *et al.* (1984b) that "though the detailed physiological basis of instrumental learning and of instrumental memory remains to be elucidated, a step in the right direction is the identification of the hippocampal complex, the high-order polymodal association cortex from which the fornix arises (Swanson, 1983), as the likely site where the higher and more specific levels of sensory analysis and of motor programmes meet for these two conceptually though perhaps not physiologically separate types of trace formation" (p. 316).

In contrast to Gaffan and co-workers, who emphasized similarities between hippocampal and fornix damage, other authors have pointed to gross discrepancies. For instance, the results of Mahut *et al.* (1982) contradicted those of Gaffan, finding no deficit in recognition memory after fornix transections, but a marked one following resections of the hippocampus. This discrepancy between the different studies remains important, though Mahut *et al.* listed the age of the animals, the use of a matching-to-sample vs a nonmatching-to-sample task and the length of the post-operative recovery period as variables which could account for it. In fact, a recent study, aimed at resolving these discrepancies, again found only a small impairment of recognition memory in fornix transected monkeys (Bachevalier *et al.*, 1985a).

Furthermore, dissociations between fornix and hippocampal lesions were also found on the behavioral level in the reports of Moss *et al.* (1981) and Zola-Morgan *et al.* (1983b). Zola-Morgan and co-workers (1983b) suggested a role of the fornix in motivation, as monkeys with sections of the fornix, but not those with ablation of the hippocampus, had

a high preference for novel stimuli in both the visual and auditory modality, even when this tendency cancelled the possibility of food reward.

7.2.2. *Combined damage of hippocampal structures*

Orbach and co-workers in 1960 already reported results of learning and retention in monkeys after combined amygdala–hippocampus resections, taking the operation protocol for H.M. as a model in which the resection was described as "extensive enough to damage portions of the hippocampus and hippocampal gyrus bilaterally" and which mentioned that "the uncus and amygdala have also of course been destroyed" (Scoville and Milner, 1957, p. 20). As only moderate impairments were then found, and mainly in those monkeys with rather extensive lesions, this approach of combined damage to the amygdala and hippocampus was not followed up until 1978 when Mishkin published the outcome of an experiment which demonstrated a severe impairment in a delayed nonmatching-from-sample task in monkeys only when the amygdala and hippocampus were removed in combination, and not separately.

Mishkin's (1978) results initiated a revival of this approach of damaging the two structures together, and as a result the deficit found by Mishkin (1978) for the visual modality was extended to the tactile modality as well (Murray and Mishkin, 1983, 1984).

Furthermore, when monkeys received bilateral damage to the hippocampus plus unilateral damage to the amygdala (or vice versa, bilateral damage to the amygdala and unilateral damage to the hippocampus) their performance in a one-trial visual recognition task lay midway between that of monkeys with bilateral damage of the amygdala or hippocampus and that of monkeys with combined bilateral damage of both structures (Saunders *et al.*, 1984). This graded relation, however, may only hold for certain kinds of learning tasks (Mahut, 1971). The amygdaloid region seems to be especially necessary for successful crossmodal association (Murray and Mishkin, 1985; cf. also Sarter and Markowitsch, 1985b).

Bachevalier *et al.* (1985b) recently suggested that the deteriorative effects of combined lesions may hold not only for the structures of the hippocampal formation and amygdaloid complex, but may be found for their main efferent pathways as well. The fibers constituting the temporal stem, on the other hand, seem to be less important for long-term information processing than was suggested by Horel (1978) (Zola-Morgan *et al.*, 1982).

7.2.3. *Spared functions*

After the so-called global amnesic syndrome was found to be less global than had been assumed at the beginning of reasearch on H.M., attempts were made to find a comparable differentiation in the monkey model (Malamut *et al.*, 1984; Zola-Morgan and Squire, 1984). Zola-Morgan and Squire (1984) described monkeys with bilateral combined amygdala–hippocampal damage which were only mildly impaired in learning relatively difficult pattern discrimination tasks, while monkeys with temporal stem lesions manifested severe impairment in this task. The authors considered pattern discrimination learning as having "a large skill-like component" (p. 1872, Abstract) and therefore assumed that they had obtained a parallel to case H.M., whose skill learning was relatively preserved as well. They based their conclusions furthermore on the assumption that the conjoint lesions of the amygdala and hippocampus in their monkeys reproduced the surgical removal sustained by H.M.

While both assumptions may prove to be correct, at present they nevertheless do not yet appear cogent. We base our reservations here on the facts that the exact location of H.M.'s lesion is unknown and that he was an epileptic patient before surgery, but also on the assumption that H.M. would have difficulties in successfully performing a pattern discrimination task similar to that learned by the operated monkeys, an assumption which is made likely by the finding that he was already incapable of learning puzzles (Scoville and Milner, 1957) or simple versions of mazes (Milner *et al.*, 1968), that is, tasks which

can be assumed to have skill-like components as well. Furthermore, the absence of a pronounced Klüver–Bucy syndrome in H.M. argues against a complete amygdala–hippocampectomy, while vice versa the lesions produced in monkeys might lead to an inter-mingling of motivational and mnemonic changes in several of the tasks employed (cf. Mahut *et al.*, 1981b).

Malamut *et al.* (1984) gave an example for the differentiation between "memories" and "habits", stressed by Mishkin *et al.* (1984) and by Mishkin and Petri (1984). They found that monkeys with combined removal of the amygdala and hippocampus were severely impaired on visual memory tasks with delays of one min or two, but learned visual discriminations as quickly as normal animals. Even with inter-trial intervals as long as 24 hr, the monkeys were able to discriminate between concurrent sets of 20 objects.

Malamut *et al.* (1984) proposed a habit formation system which did not rely on limbic brain structures to account for the unimpaired performance of their monkeys with such combined lesions (Mishkin *et al.*, 1984; Mishkin and Petri, 1984).

7.3. Other Animal Models of Human Amnesia

A number of further attempts were made to simulate human amnesia in animals, though they were usually less specific than those reviewed above, most of which were intended from the beginning to replicate the mnemonic behavior of H.M. For instance, electrical brain shock was applied in animals in order to test for effects similar to those found in patients after electroconvulsive therapy (see Section 3.4.2) (Gold *et al.*, 1974a,b, 1975; Lewis *et al.*, 1968, 1969; Martinez *et al.*, 1981). Other authors have sought for relations between performance and alterations in the biochemistry of the brain (e.g. Flexner and Flexner, 1969; Gold and Sternberg, 1978; Gold and Zornetzer, 1983); for ultrastructural changes in specific brain regions following learning (Wenzel *et al.*, 1977a,b); for changes after cerebral ischemia (DeGirolami *et al.*, 1984; Garcia *et al.*, 1983; Kirino, 1982), induced viral infection (Bak *et al.*, 1977; Cook and Stevens, 1973; Scott and Fraser, 1984) or thiamine deficiency (e.g. Irle and Markowitsch, 1982c; Witt and Goldman-Rakic, 1983a,b) (Fig. 26) in animals, or have tried to imitate dementic processes such as Alzheimer's disease (Bartus, 1982; Crapper and Dalton, 1973a,b; Crapper *et al.*, 1973; Friedman *et al.*, 1983; Kessler *et al.*, 1986; Mishkin *et al.*, 1982; Salamone *et al.*, 1984).

The main body of results from this last mentioned approach is as yet rather preliminary since rats are still able to acquire tasks such as place learning, even when delays of up to 2 hr are interposed between trials (e.g. Kessler *et al.*, 1986) and in spite of well-centered lesions (Figs 27 and 28).

Parallels between certain aspects of the amnesic syndrome of humans and the performance of rats were described by Kesner and Novak (1982) and by Thompson (1981). Kesner and Novak found that normal rats exhibited a so-called serial position curve, that is, they remembered well the first and the last items in an eight-arm radial maze, while rats with hippocampal lesions only showed a recency effect (remembering the last but not the first item). Furthermore, the introduction of a 10 min delay abolished both the primacy and the recency effects. Results similar to those of Kesner and Novak were also found in rats with lesions of the thalamic mediodorsal nucleus when tested in a six-arm maze (Fig. 29) (Kessler *et al.*, 1982b).

Thompson (1981) found that rats with hippocampal lesions subjected to spatial reversal learning exhibited rapid forgetting, while rats with lesions of the mamillary bodies disclosed only very little. Thompson argued that for the rat, memory defects are reliably seen only in spatial tasks (cf. also Kessler *et al.*, 1982b; Olton, 1977; Olton *et al.*, 1979; Olton and Papas, 1979; Walker and Olton, 1984). While this may be correct, in our view it points out again some discrepancies between the amnesic syndrome of human and nonhuman species (cf. Section 7, Weiskrantz, 1982b). Such discrepancies can also be seen in the results of recent experiments designed specifically to yield complete lesions of memory-related brain structures (see next section).

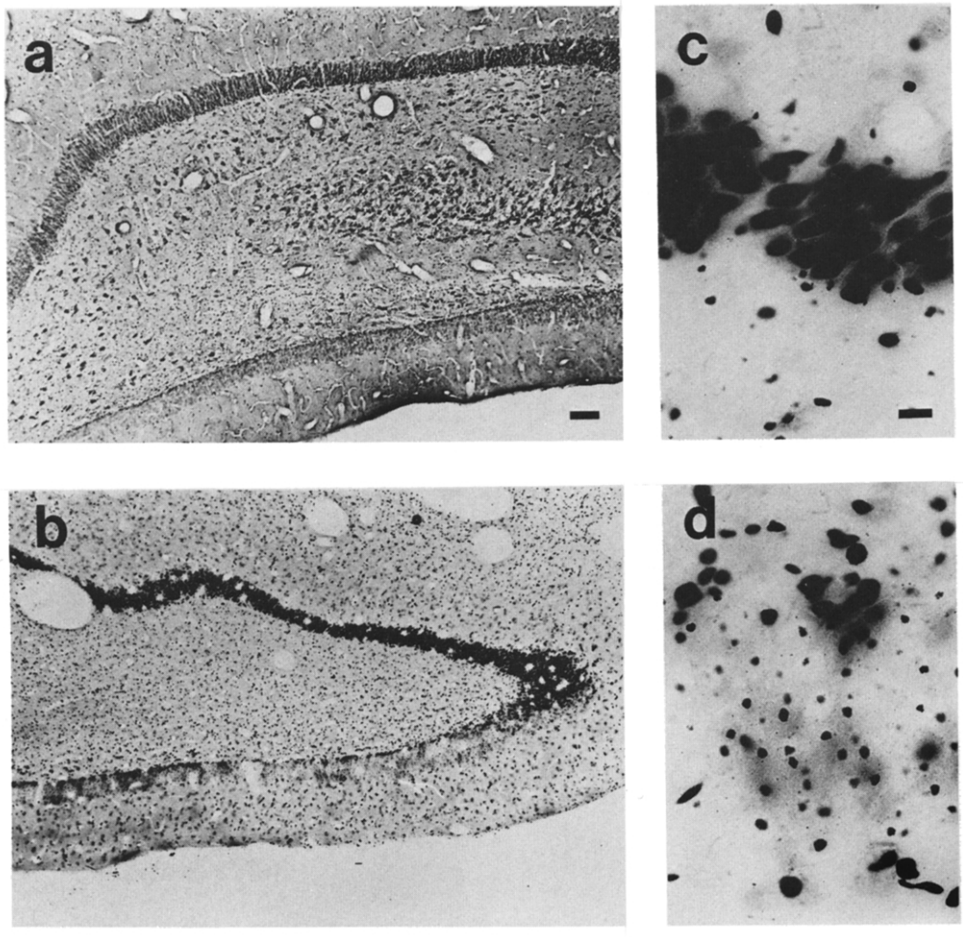

FIG. 26. Appearance of neurons in the region of the granular layer of the hippocampus in a Nissl stained section (a) and in reduced silver stained sections (b)–(d) from the brain of a cat given a thiamine-deficient diet (Irle and Markowitsch, 1982c). Note the damaged granular neurons next to the ventricular space in (a), (b) and (d); for comparison with (d), part (c) of the figure shows the normal appearance of the granular cell layer somewhat farther away from the ventricular space (parts (c) and (d) are both from the section shown in (b)); scale bar in (a) is 100 μm and also holds for (b); scale in (c) is 10 μm and holds also for (d).

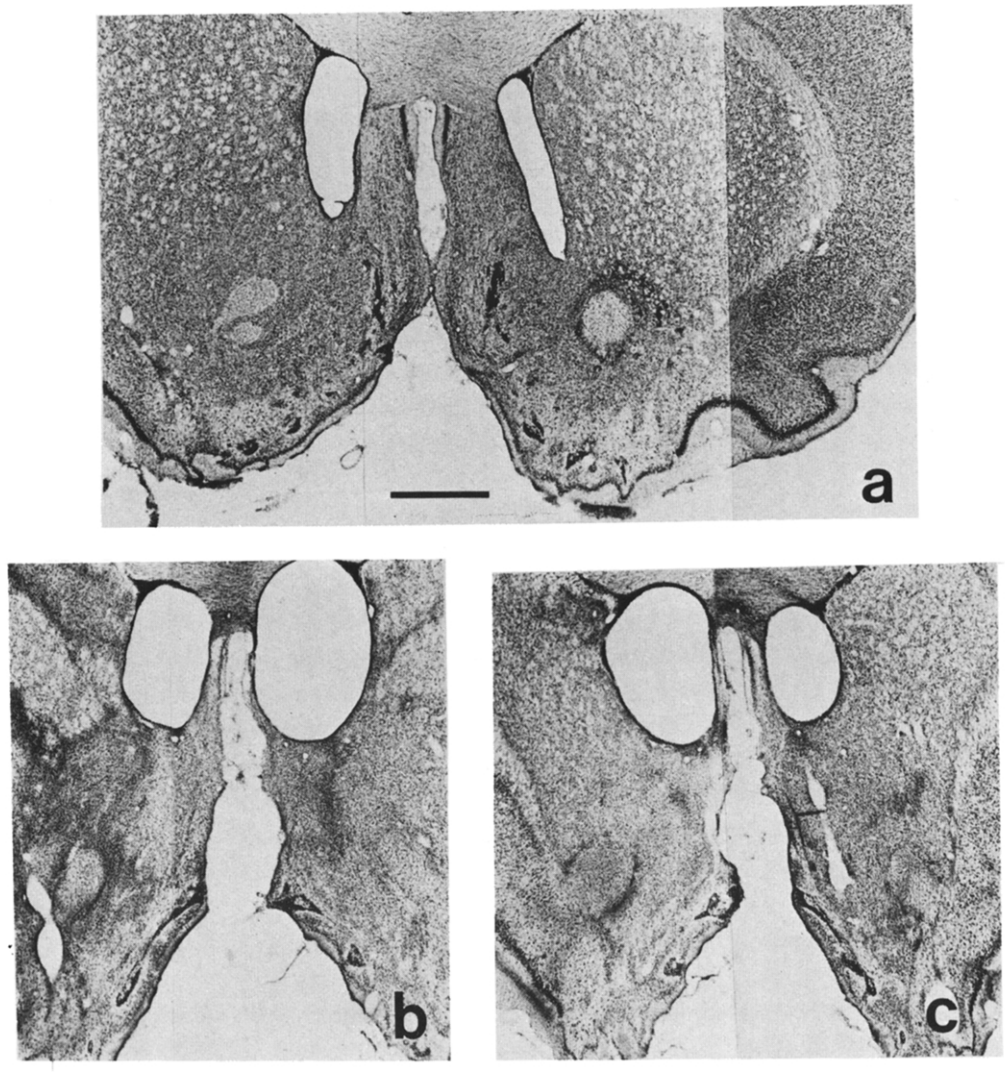

FIG. 27. Nissl stained coronal sections through the rat brain showing ibotenic acid-induced lesions of basal forebrain regions, namely the diagonal band of Broca (a) and the medial septal area (b), (c); scale bar in (a) represents 1 mm and holds also for (b) and (c). Rats with such lesions were impaired in acquiring delayed spatial tasks, but in most cases did finally learn them (data from Kessler *et al.* (1986)).

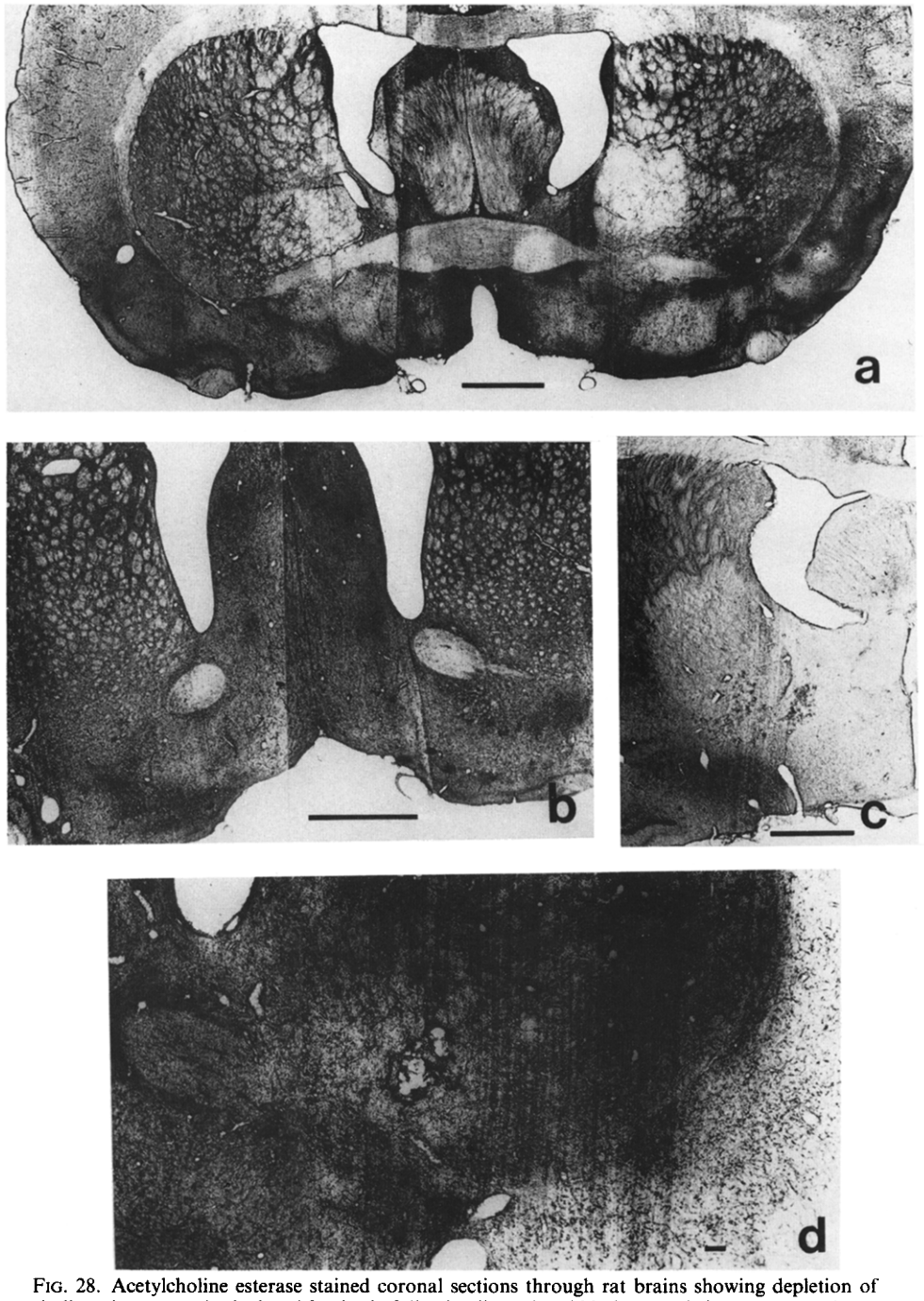

FIG. 28. Acetylcholine esterase stained coronal sections through rat brains showing depletion of cholinergic neurons in the basal forebrain following ibotenic acid lesions, scale bars represent 1 mm in (a)–(c) and 100 μm in (d). Rats with such lesions were impaired in delayed spatial tasks, but in most cases did finally learn them (data from Kessler *et al.* (1986)).

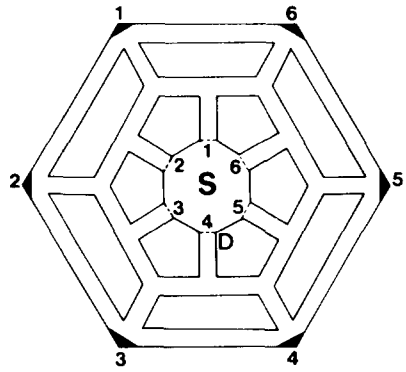

FIG. 29. The radial arm maze version used by Kessler *et al.* (1982b). The center field is labeled S (start), the doors are numbered 1 to 6, as are the goals (solid triangles). (Goal 1 and 6 are next to Door 1.) The task of the rat is to approach each of the six goals in succession to receive the reward placed there, repetitions are errors which are not rewarded. Normal rats are very successful in performing this task, while rats with hippocampal lesions show marked impairments in mazes of this kind, and rats with lesions of the thalamic mediodorsal nucleus show moderate, but still clearly memory-related impairments. (The figure is reproduced from Fig. 1 of Kessler *et al.* (1982b).)

7.4. MASSIVE BRAIN LESIONS

While a mass effect of brain lesions on behavior has face validity and was proposed at least since the times of Lashley (1929), there is also counter-evidence against this view from rather different sources (e.g. Finger and Stein, 1982; Nathan and Smith, 1950; Sprague, 1966).

Irle and Markowitsch (1983a), for example, were interested in extending their earlier findings on memory impairments after selective diencephalic lesions (Irle and Markowitsch, 1982d; Markowitsch, 1982b) by performing lesions of the whole modified Papez circuit (as defined in Irle and Markowitsch, 1982a). Contrary to expectation they found that the combined destruction of the subicular cortex (that part of the hippocampal formation from which the main body of the fornix fibers originates) and of the mamillary bodies and the anterior thalamic nuclei failed to result in deficits in the acquisition of a visual discrimination task or of two reversals of it, while a destruction of only two of the three structural complexes (in any combination) resulted in significant deficits compared to a control group.

The authors confirmed and extended these results by showing that a group of cats with lesions of the three structures of the modified Papez circuit (cf. Fig. 6) plus the pre-frontal cortex was similar in learning performance compared with a control group and a group which received only pre-frontal cortical lesions (Irle and Markowitsch, 1984a). As can be seen from Fig. 30, the cats with four-fold lesions were unimpaired compared to the control animals in the original acquisition of a reversal task as well as in two reversals of it, furthermore, they were unimpaired (or even better) compared to the control group in acquiring a two-way active avoidance task. Deficits were only seen in spatial alternation and spatial delayed alternation—two tasks sensitive to pre-frontal damage.

These results are in strict opposition to what would be expected from most of the available data on the human amnesic syndrome and on animals with selective lesions in imitation of the human amnesic syndrome. Nevertheless, hypotheses can be formulated to explain these findings, as was done in Irle and Markowitsch (1983a, 1984a), and, in more detail, in Markowitsch (1985a).

Irle and Markowitsch (1983a) proposed the existence of more than one circuit involved in the processing of mnemonic information for long-term storage (and/or retrieval). They furthermore suggested that these circuits are ordered hierarchically so that only the complete destruction of one circuit brings the other, subordinate one, into action (Fig. 31; cf. also Fig. 2 in Markowitsch, 1985a).

According to the assumption of Mishkin *et al.* (1984), Mishkin and Petri (1984) and

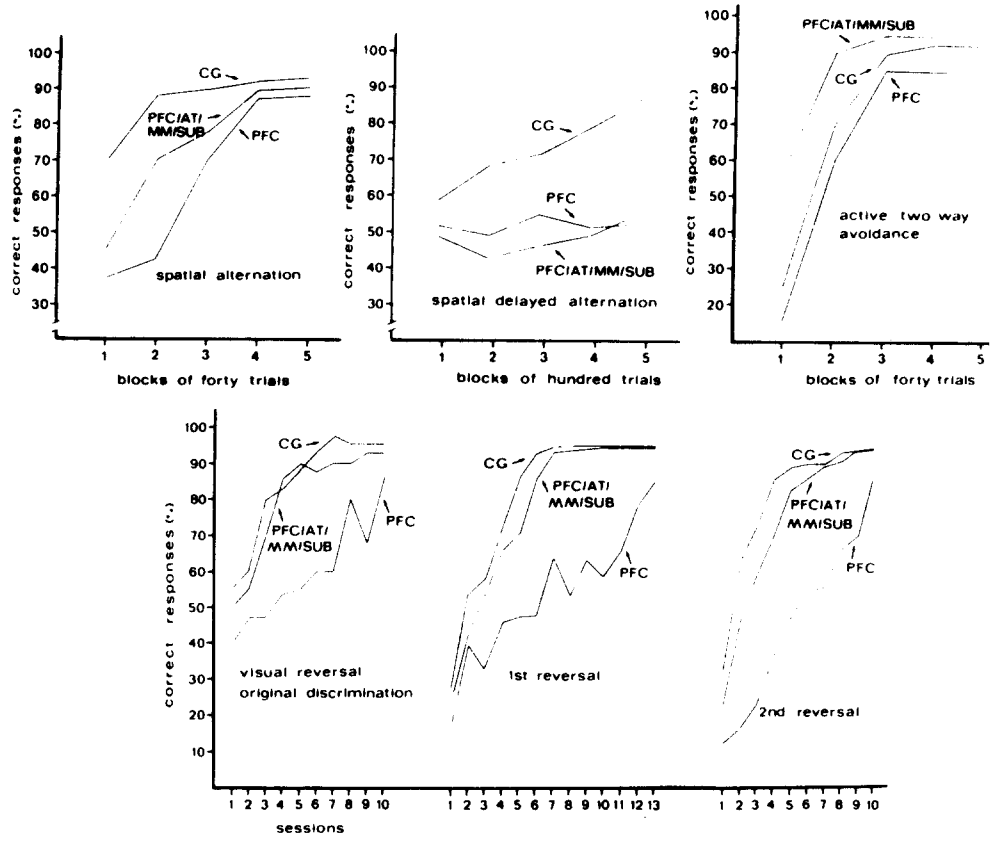

FIG. 30. Learning curves of cats in a control group (CG), cats with four-fold lesions, including the pre-frontal cortex, the anterior thalamus, the mamillary bodies and the subiculum (group PFC/AT/MM/SUB) and cats with pre-frontal lesions alone (group PFC) in the acquisition of the learning tasks indicated. The curves demonstrate the similar acquisition rates of the pre-frontal-lesioned cats and the cats with four-fold lesions (as opposed to control animals) in the 20 sec delayed alternation task, the somewhat superior acquisition rates of cats with four-fold lesions in the active two-way avoidance task and the striking similarities of the cats with four-fold lesions and the control cats in the three stages of the visual reversal task shown. (After Fig. 7 from Irle and Markowitsch (1984a), reproduced with permission.)

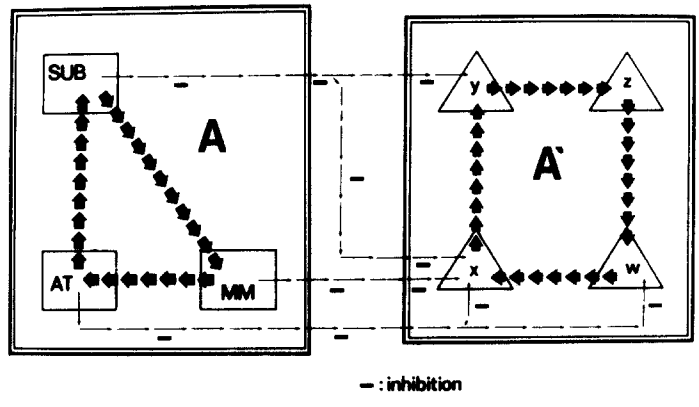

FIG. 31. Highly schematized diagram for demonstrating the way in which a dominant and a subordinate brain circuit might interact in the same behavior. Circuit A is assumed to be composed of the mamillary bodies (MM), the anterior thalamus (AT) and the subiculum (SUB). It is assumed that each of the three structures is able to inhibit the action of circuit A′ (symbolized by the structures w, x, y, z). In this diagram the inhibition acts on only three of the four structures; it may, however, just as well act on only one structure or on all of them (or in any other logical constellation). Consequently, disinhibition of A′ occurs only if each of the three structures belonging to circuit A has been destroyed. (Reproduced from Fig. 8 of Irle and Markowitsch (1983a).)

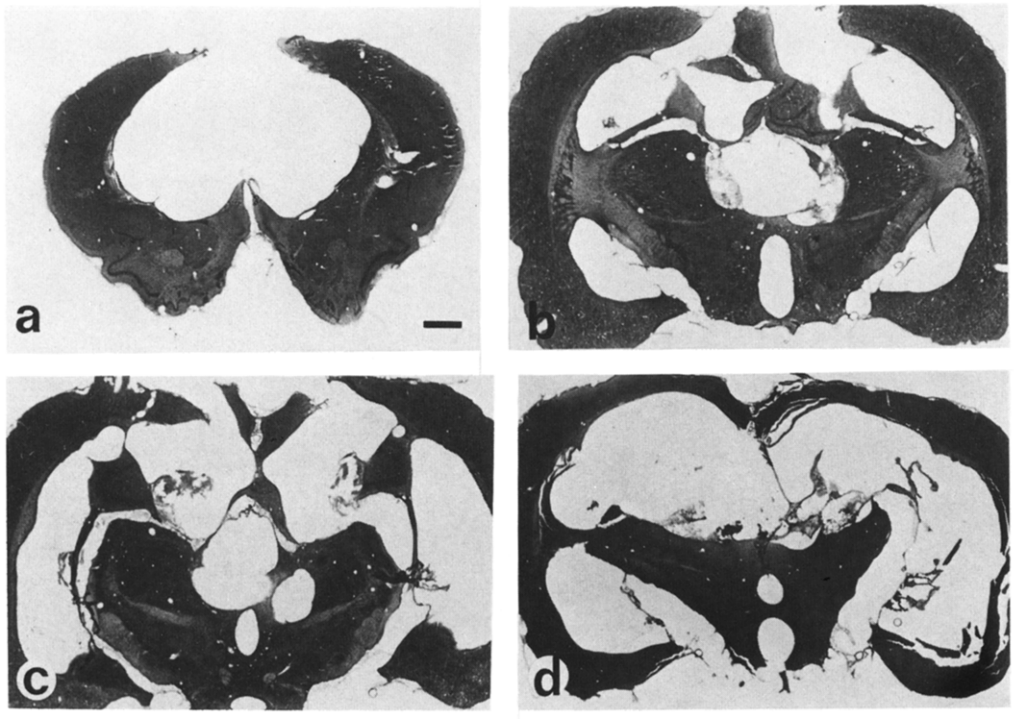

FIG. 32. Example of a rat brain with cortical ((a), (b)), hippocampal ((b)–(d)) and thalamic ((b), (c)) lesions from the study of Markowitsch *et al.* (1985). Scale bar in (a) represents 1 mm and holds also for (b)–(d).

Pandya and Yeterian (1984), different circuits exist for different mnemonic processes (such as, e.g. spatial or habit-related vs nonspatial or event-related information). A complete destruction of the hierarchically highest unit disinhibits the subordinate one so that the latter can come into action, and this results in less behavioral deficit than a more selective, incomplete lesion would, which only leaves the primary circuit with reduced possibilities for information handling, but which cannot yet activate or disinhibit the subordinate one.

Both a genetic pre-disposition and (early) environmental influences might be given as possible explanations for the existence of such hierarchically ordered selection units. The importance of the environment in altering brain activity, possibly including even morphological changes, was stressed in a number of more recent experiments (Bennett, 1976; Denenberg *et al.*, 1978; Diamond *et al.*, 1975; Freed *et al.*, 1985; Innocenti and Clarke, 1984; Uphouse, 1980; Walsh and Cummings, 1975). Furthermore, recent studies (as well as some older ones) argue for the existence of important individual differences which can be seen not only during development (e.g. Fischer and Silvern, 1985; Horowitz, 1969; Wachs, 1984), but also in the electrical activity of the brain (e.g. Daruna and Karrer, 1984), the response to lesions (e.g. Oscar-Berman, 1984) and in the morphology of the brain (e.g. Fischer, 1921; Merzenich *et al.*, 1975; Webster, 1981).

How environmental influences, brain damage and inter-individual differences may contribute to the memorizing of a learning task was recently demonstrated by Markowitsch *et al.* (1985a) who tested the ability of seven groups of rats to acquire or to relearn tasks under different conditions: after being subjected to multiple brain lesions, namely in (1) the medial pre-frontal and cingulate cortex, (2) the anterior and mediodorsal thalamic nuclei and (3) the dorsal and ventral hippocampus (Fig. 32). Rats of Group 1 received the cortical, thalamic and hippocampal lesions in succession and were then trained in a delayed alternation and an active two-way avoidance task. Nine of 10 animals, all with considerable damage to each of the three structural complexes, failed to acquire delayed alternation within 1,000 trials, while most of them were able to learn the avoidance task. Animals of Groups 2, 3 and 4, which received lesions of only two of the three complexes, were able to learn either task.

Animals of Groups 5 to 7 first acquired both tasks and were then given lesions in all three target areas in three different operations. Animals of Group 5 received retraining to criterion with a maximum of 1,000 trials following each of the three operations. Animals of Group 6 were given a short period of 240 trials of overtraining and then had to relearn the tasks after having received the three brain operations in succession, while animals of Group 7 were given that amount of overtraining prior to any surgery which corresponded to the averaged number of trials which animals of Group 5 needed during their intermittent delayed alternation training (between operations), namely 1,280 trials. It was found that (1) considerable inter-individual differences in relearning existed between animals despite basically rather similar lesions, and (2) that the rats with the large number of trials in pre-operative overtraining were practically unimpaired post-operatively, while half of the 10 animals of Group 5 failed to learn the delayed alternation task, four of them already after only the second, thalamic, lesion (Fig. 33).

These results therefore point to the importance of environmental influences in complex information processing and offer support to the hypothesis that between brains different modes of mnemonic information processing may exist which evolved at least in part through environmental influences, and which may lead to considerable variances between individuals with comparable brain damage.

7.5. INFERENCES FROM THE ANIMAL MODEL

Research on relations between brain damage and memory processing in animals has provided a number of parallels to and confirmations for respective inter-relations in the human being. One of the most important contributions of research in animals is, of course, the establishment of the "wiring diagram" of the brain, that is, the determination of which areas are connected via pathways with each other. This kind of research has led to the

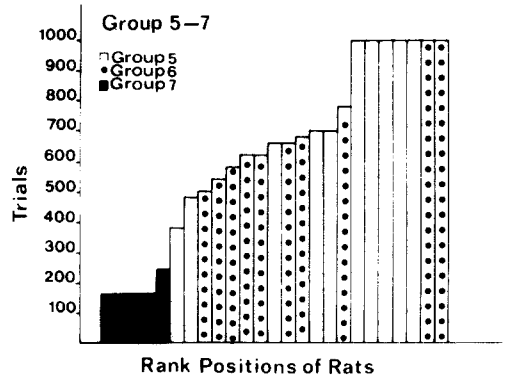

FIG. 33. Performance of individual rats in Groups 5 to 7 during relearning of delayed alternation after massive cortical, hippocampal and thalamic lesions as shown in the example of Fig. 32. Rats of Group 5 relearned the task following each of the three brain operations (or were excluded from further learning after 1,000 trials); rats of Group 6 were given 240 trials of overtraining prior to any surgery, but no training between lesions and rats of Group 7 were given 1,280 trials of overtraining prior to any surgery, and likewise no training between lesions.

grouping of specific regions and shown how information is probably distributed or converges, allowing inferences on possible channels of information processing and on the manner of serial and parallel transmission of signals.

Furthermore, it has provided an additional basis, aside from cyto- and myeloarchitecture, for dividing areas and subareas, and therefore also for determining which regions should be lesioned for any individual animal.

Related to this approach is the comparative one which investigates structures, pathways, biochemical effects and lesion–behavior relations between different species. Similar findings across a number of species, especially mammals, provide one method for inferring to the respective situation in the human being, and transferring any information to humans is especially useful when trends or directed ("phylogenetic") developments are apparent within the nervous system in species which can be considered to represent more ancient ancestors up to those which have strong similarities to humans (such as apes).

An example of such a directed development can be seen in the hippocampal formation. On the one hand this structural complex is an ancient attribute of the mammalian (and, more generally, even of the vertebrate) brain, but, on the other hand, it has changed considerably between, for example, rats and rhesus monkeys in structure and in its connections and most likely in its roles for controlling behavior (see Brodal, 1969; Jacobs *et al.*, 1979; Markowitsch, 1985d; Morgane *et al.*, 1982; Stephan, 1975). In fact, the strong involvement of the rodent hippocampus in spatial behavior (cf. Section 7.3; O'Keefe, 1979; O'Keefe and Conway, 1978; Olton *et al.*, 1978) but, on the other hand, the lack of spatial disabilities following hippocampal removal in humans demonstrates the extent to which structural complexes may change their role in behavior across species.

Due to the probability that one and the same brain structure will have some important differences in anatomy and functional involvements across mammalian species, it is, of course, most promising to use nonhuman primates as heuristic models for investigating inter-relations between the human brain and behavior. This statement seems to be particularly true for the investigation of memory and its disturbances. Because research on mnemonic functions in humans emphasizes the existence of several kinds of mnemonic abilities (e.g. Tulving, 1985) and is involved in relating specific brain areas to specific mnemonic functions (e.g. Graf *et al.*, 1985; Nebes *et al.*, 1984; Squire and Zola-Morgan, 1983; Weinhartner *et al.*, 1983), the use of primates for the investigation of brain–memory relations becomes all the more important.

The present review on animal models of human amnesia has shown that the brains of animals and those of humans are vulnerable to similar intoxications and interventions (the effects of thiamine deficiency on hippocampal neurons, seen in Fig. 26, can serve as an example). However, while the changes in morphology following various treatments are

probably rather similar to those seen in human beings, the behavioral consequences in animals may resemble those seen in humans only to some lesser degree and may even show qualitative dissimilarities for certain brain–behavior relations. On the other hand our view of the possible action of the mammalian brain in controlling behavior has been widened by research on combined or multiple lesions and especially by recent work on primates with various lesions. With respect to this approach—investigating the degree of communication among large neuronal assemblies and the combined reaction of brain structures and the possible occurrence of imbalances in the neuronal network following rather small brain lesions—some results offer a promising new understanding of the action of both the intact and the damaged mammalian brain in long-term information processing.

8. Conclusions

Damage to a variety of brain structures can be followed by memory disturbances. While these may be more selective in character or less lasting in time following restricted neocortical damage, the affection of limbic system-related structures, or diencephalic and telencephalic regions situated close to liquorous spaces (cf. Fig. 26) may lead to a more global deterioration of mnemonic abilities, in particular those regarding the acquisition of new information.

After a variety of possible causes of brain damage (such as, for example, changes in blood supply, the development of cysts or neuronal degeneration), severe mnestic disturbances, at least in adults, will usually follow the involvement of rather circumscribed brain areas in a way that to a certain degree even allows a differentiation between amnesic forms on the basis of the most severely affected brain regions.

While the present review provided a number of examples in support of this view we nevertheless wish to recall some results incompatible with the hypothesis of a specific brain region–memory alteration relation. Examples of such cases, mentioned before, include N.A. (with a probably rather specific, unilateral lesion in the medial dorsal aspect of the thalamus and lasting anterograde amnesia for verbal material), and those cases with bilateral stereotaxic lesions in the same thalamic area, but with at most only transient mnemonic alterations (Orchinik, 1960; Wycis, 1972). Further examples can be found in the literature on the effects of brain lesions in infants or juveniles, and on congenital neuronal malformations.

Within certain stochastic limits modern neuropsychology is nevertheless capable of predicting the consequences of distinct brain damage on memory alterations and permits a distinction between certain forms of amnesia and dementia. These statements hold in particular for recent memory disturbances, while there is still only rather limited knowledge on the neuropathology of lasting retrograde amnesia.

While it has become commonplace now to speak of *two* forms of amnesia (Squire, 1981) and to relate them to medial temporal lobe or diencephalic damage (Squire, 1980, 1981, 1982a), the recent descriptions of severely amnesic cases with primarily basal forebrain damage attenuate such claims. We are therefore still at the level of knowing that distinct brain damage can lead to a severe and lasting mnestic change, but our hypotheses on the specific inter-relationships between brain regions (either the neurons themselves or their connections) are not yet established, although it is just this total inter-relationship that determines the final behavioral deficits and not merely the punctual tissue damage apparent in computer tomography or in post-mortem inspection of the brain. Animal research may be of considerable help in promoting this kind of approach. For instance, combining permanent and/or temporary lesions of several brain regions (e.g. by the cooling method) may reveal how restricted neuronal assemblies interact and how memory processing depends on mutual communication between brain regions.

9. Summary

Relations between brain damage and memory disturbance are outlined with emphasis on the so-called amnesic syndrome. Following a brief introduction into forms of memory

and memory failures, the basic causes of brain damage (with relevance to mnestic failures) are described. Thereafter, the two best-known forms of brain damage–amnesia relations are reviewed: the consequences of damage to medial temporal lobe structures and to diencephalic regions. For the cases with medial temporal lobe damage, evidence is reported in greater detail for H.M., who has been examined more than any other amnesic patient for more than 30 years now, as a considerable amount of literature has accumulated on his behavior in diverse situations.

Other cases with more or less circumscribed damage to medial temporal lobe structures are reviewed so as to outline criteria for or against the hypothesis that there are regions within the medial temporal lobe whose damage might be critical for the amnesic syndrome.

Two cases of diencephalic amnesia are summarized in particular (cases of Mair *et al.*, 1979) as they have received extensive neuropsychological and neuropathological investigation. Other cases with, for example, Korsakoff's disease are reviewed, as well as cases with diencephalic, or combined mesencephalic–diencephalic damage without nutritional causes.

A third group of patients with massive, but still selective amnesic disturbances are then described: cases of basal forebrain damage, followed by descriptions of Alzheimer's disease which has similarities in the underlying neuropathology. This leads over to cases with more generalized intellectual deteriorations (dementia), which may have developed on the basis of primarily cortical damage or damage principally to basal ganglia structures.

After reviewing cases with mainly material-specific memory failures—usually as a consequence of restricted neocortical damage—a separate section follows on patients in whom retrograde amnesia is the prominent symptom.

The contribution of animal models of human amnesia is critically reviewed and discrepancies are analyzed between human and animal memory disturbances. This section emphasizes the value of investigating inter-dependencies between brain structures by pointing out that relations between memory disturbances and brain damage may be more complicated than apparent from a simple structure–function assignment. This aspect is further followed up in the conclusions.

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