CHAPTER 30
Learning, Memory, Amnesia, Dementia, Instinctive Behavior and the Effects of early Experience

DEFINITIONS

(1) **Learning:** a relatively permanent change in behavior that results from practice or experience. Learning is the process of acquiring knowledge about the world (Kupperman, 1991). This definition implies plasticity in central nervous system function and it also implies plasticity in the formation of stimulus response connections. The definition excludes changes in behavior result-ing from maturation, sensory adaptation and fatigue.

(2) **Memory:** the processes or neural mechanisms involved in the encoding and storage or repre-sentation of an experience and the retrieval of that information. At times the definition is restricted to the "read in" consolidation and storage stages and the terms remembering and retrieval are defined as the "read out phase" of learning.

(3) **Instinctive behavior:** complex behavior occurs on the first presentation of the triggering stimulus. Such behavior occurs in all species even those raised in isolation. In birds, complex behavior may be triggered by hypothalamic or midbrain stimulation.

(4) **Imprinting:** Not all behavioral patterns are learned or instinctive. *Certain behavioral patterns require exposure to a specific stimulus at a critical period in development.* The concepts of imprinting evolved from the study of "following" behavior in newly hatched chicks. Thus, chicks will usually follow their natural mother since during the specific critical period after hatching they are usually exposed to the mother. However, if chicks do not encounter the mother but rather encounter a man, they will tend to follow the man. Critical periods in human postnatal development have also been demonstrated.

(5) **Disorders of memory:** This problem may reflect focal or more generalized disease of the nervous system. The process may be static or progressive. Included in the definition in addition to the focal disorders involving hippocampus and diencephalon are more generalized disorders such as dementia, amentia and mental retardation.

(6) **Dementia:** *A progressive impairment* of previously intact mental faculties without loss of consciousness. In general, in the most common type, Alzheimer's disease, the loss involves initially and most severely recent memory and the ability to learn and retain new memories. To some extent, particularly as time passes, other areas of mental capability are also affected: remote memory, abstract reasoning, insight, arithmetic abilities, language function, personality mood and social behavior. In other types personality is initially affected, followed later by memory.

(7) **Amentia:** The term amentia implies a *non-progressive congenital absence or relative deficiency of mental faculties.* At times, in the absence of an adequate history, the distinction may be difficult to make. The term **mental retardation** is somewhat less specific, referring to retardation in the development of mental abilities or retardation in the development of intelligence.

LEARNING IN MAN AND RELEVANT ANATOMICAL SUBSTRATE

Classification of learning and the anatomical substrate: (Squire & Zola-Morgan, 1991, Desimone, 1992, Rolls, 2000). Essentially two broad categories are considered:

I. **Declarative (Explicit) learning** - This refers to the conscious recollection of facts or events. This system is rapid; one trial may be sufficient.

II. **Non-Declarative (Implicit or "Reflexive")** - This refers to a non-conscious

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alteration of behavior by experience. This type of learning is slow and requires multiple trials. Table 30-1 presents the neural substrate for these types of learning

STAGES OF HUMAN MEMORY: DECLARATIVE LEARNING

The terminology employed has changed with time particularly as regard the terms short term and long-term memory. As presented in table 30-1, there are essentially three major stages.

Immediate or short term working memory– This stage has been discussed in chapter 18.This is a matter of seconds (estimated as <10 seconds. Total capacity has been estimated as less than 12 items. It is best exemplified in simple digit repetition as in digit span testing or the immediate repetition of three or 5 objects or the **delayed response test** utilized in monkeys and children. Monkeys with prefrontal lesions and infants less then 8 months (presumably with immaturity of the frontal function) are unable to consistently perform the task. The neural substrate undoubtedly involves the reception in the appropriate primary sensory projection area with relay to the adjacent sensory association cortex; for example, areas 18, 22, 5/7 then transfer to the multimodal posterior parietal cortex, then relay to prefrontal area for very short term storage and then relay to motor association cortex and then to motor cortex if the information is to be recited to the examiner (as in the digit span or immediate recall tests).

Long-term memory. Labile stage - This stage may be considered a transcription and transduction stage. The duration of this intermediate process has been variously estimated in infrahuman species as a matter of 20 to 180 minutes. The time required is probably shorter as one descends the phylogenetic scale. Theoretically, this stage involves the transcription from a relatively localized reverberating neuronal circuit, indicated in the immediate memory stage, into a more permanent macromole-cular form of recording. It has been hypothesized that RNA and protein synthesis

TABLE 30-1 TYPES OF LEARNING AND NEURAL SUBSTRATE

TYPE	ANATOMICAL SUBSTRATE
I Declarative: conscious,facts or events	
-Stage 1: short term/ working/immediate memory	Prefrontal
-Stage2: long term memory: labile stage (Transcription/ transduction and consolidation)	Limbic system: hippocampus-thalamus
-Stage 3: long term memory: stage of remote memory	Diffuse cerebral cortex
II Non Declarative: non conscious, reflexive	
- Motor habit and skill learning	–Cerebellum, striatum and motor cortex.
-Classical and operant conditioning	-Amygdala for emotional responses, -Cerebellum for motor responses
-Non associative learning: Sensitization*/ habituation)**	Reflex mechanisms of spinal cord and brain stem
-Priming: recall of words/ objects improved by prior exposure to these stimuli	Neocortex

*Sensitization=increased response to non noxious stimuli after presentation of noxious stimulus

**Habituation=decreased response to a benign stimulus when this is presented repeatedly

are involved in this stage. It should be noted that RNA turnover does increase in tissues undergoing learning-like experiences. RNA turnover also increases in areas of neural tissue subjected to repetitive stimulation. It is clear that interference with RNA synthesis or with protein synthesis (by the use of the antibiotic puromycin) interferes with this stage of memory. Presumably, as we will discuss below, an accompanying change in synaptic connection is beginning to occur.

The neural structures involved are the entorhinal cortex, parahippocampal gyri, the hippocampus, the fornix, and the anterior and dorsal medial nuclei of the thalamus. (see

Zola-Morgan and Squires, 1990, and below). These structures are inter-related as the "limbic system" previously discussed. From a clinical standpoint, we evaluate this stage of memory with delayed recall test (list of 5 objects to be remembered for 5 minutes)[1] and by asking the patient to recite a paragraph ("cowboy"or "gilded boy story") that he has just read or heard. This ability to learn and to retain new experiences and new material is often referred to as retentive memory. Disturbance of this stage in memory will be considered later under the topic of the amnestic-confabulatory syndrome.

Long-term Memory: stage of Remote Memory - This phrase is not discretely localized. Rather, it represents a diffuse storage throughout the cerebral cortex and possibly other areas of the central nervous system. Long-term memory would appear to relate more to the actual volume of cortex remaining intact than to any specific localized process (consistent with the concept of Lashley). Although not discretely localized, it must be recalled that the read out mechanism for such remote memories may be triggered by stimulation of the lateral aspect of temporal lobe in the particular abnormal situation of patients who are subject to complex partial seizures of temporal lobe origin (refer to Chapter 22). In such patients, ablation of the area that on stimulation produces the remote memory does not abolish this remote memory. From a clinical standpoint, we evaluate this stage of memory asking the patient to indicate his date of birth, date of marriage, dates of World War I and II, and so forth.

FACTORS INFLUENCING LEARNING AND MEMORY

In the consideration of the learning process, it is important to realize the influence of several additional factors.

(1) **Motivational drives** alter the rate of learning. There are primary or instinctive drives such as hunger thirst, sex present in all members of a species, irrespective of cultural influences and in general present in the infant. There are learned, secondary drives or motivational forces such as achievement, anxiety, and dependency. These are learned drives in the sense that motivations, such as desire for acquiring money and fame, or particular fears or guilt are not present in the infant and are not present in all members of a species. During the process of development, previously neutral cues may become attached to primary drives and take on the capacity to motivate performance. Some drives such as severe anxiety may trigger responses that are not goal-directed, thereby interfering with learning. In contrast, lesser degrees of anxiety may motivate performance.

2. Motivation also affects the central process of interpretation of stimuli (perception). In a sense, what we see depends upon what we wish to see and upon our frame of reference particularly where the stimulus is ambiguous.

3. Whether stimuli are perceived will also depend on the general state of attention or alertness of the individual mediated by the reticular formation. In addition prefrontal and parietal cortex influence attention.

4. At times retention may be intact but the search and read out mechanism may be temporarily defective. This may account for the phenomena of shrinking retrograde amnesia following head trauma.

NEUROBIOLOGICAL MECHANISMS IN MEMORY AND LEARNING -

The psychologist, Hebb, in 1949 had proposed that when in associative learning the axon of neuron A - fires synapses on neuron B in a persistent manner, a growth process or metabolic change occurs in one or both neurons such that the probability or efficacy of neuron A firing neuron B is significantly increased. Subsequent studies (reviews of Kandel & Hawkins, 1992, Kandel & O'Dell, 1992) have confirmed these observations and demonstrated that the synaptic connection between neuron A and B could be strengthened by a third (modulatory neuron) – acting

[1] *Other tests utilize 3 objects for 3 minutes.*

to enhance - release of transmitter from the terminals of the presynaptic neuron. If neuron A and the modulatory neuron -discharged simultaneously, then the connection between neuron A and B would also be strengthened in an associative manner in a variety of classical conditioning and in the hippocampus in relationship to spatial learning. Subsequent studies indicated that eventually the number of presynaptic terminals was increased providing an anatomical basis for this type of learning.

Long-term potentiation: Bliss and Lomo (1973) demonstrated that brief, high frequency trains of action potentials within each of the three major pathways of the hippocampus would produce a long lasting increase in synaptic strength in that pathway lasting for hours in the anesthetized animal but for days and weeks in the alert, freely moving animal. The CA3 to CA1 Shaffer collateral pathway and the perforant-afferent pathway to the dentate gyrus have associative learning properties and the model of Hebb is followed. The pre and postsynaptic neurons must fire simultaneously. The transmitter involved is glutamate. Both NMDA and non-NMDA receptors are involved. Similar long-term potentiation has been subsequently demonstrated in other areas of cerebral cortex. The basic point to be made is that long-term potentiation provides a possible mechanism for the labile period of memory - the transition period which maintains memories for hours, days and weeks, while more permanent transduction is occurring in terms of protein, RNA, etc.

PLASTICITY IN THE NERVOUS SYSTEM

(1) **Mirror focus:** Repeated experimental focal seizure discharge with repeated transcallosal response will produce changes in the excitability of the contralateral hemisphere so that eventually an independent focal disharges develops.

(2) **Kindling:** Repeated subthreshold stimulation of the amygdala or hippocampus, or of the frontal cortex in many species will over time alter the excitability of widespread cortical area so that eventually spontaneous seizures occur. Both the mirror focus and kindling have been proposed as possible demonstration models of long-term synaptic changes that may be involved in learning. That is, the alteration of neuronal function as a result of experience.

(3) Modification of cortical motor and sensory maps. (See chapter 17). These maps are not fixed but instead have a plasticity, which can be modified by experience.

(4) **The corpus callosum also has a role in learning.** Thus, a monkey or human trained to carry out a task with one hand, e.g., how to follow a maze or somatosensory discrimination, for roughness, etc., does not have to relearn that task when the other hand is utilized – a rapid transfer of the learned skill or discrimination has occurred.

(5) **Early Experience And Postnatal Brain Development** (Refer to Spitz, 1945, Harlow, Lewis et al 1990, Siegel et al, 1993, Martine al 1991, Sirevaag& Greenough, 1985, 1987, Hubel &Wiesel, 1963). A number of studies have demonstrated a significant effect of early environment of the infant animal or human at critical periods on later brain development and function. These observations may be related to the phenomena of imprinting. Beyond a certain critical age of 15 months in the human infant, and 6-12 months in the infant monkey these changes related to environmental deprivation are irreversible. Cultural deprivation at a somewhat later stage of childhood may also produce long-term effects on psychological development. These studies also demonstrate correlated changes in the microscopic structure and biochemistry of the cortex, or basal ganglia or hippocampus. These considerations provide a biological foundation for the use of "head start" programs in preschool and primary grade students from culturally deprived backgrounds. (Refer to Hellmuth, 1968.)

DISORDERS OF RECENT MEMORY: THE AMNESTIC-CONFABULATORY SYNDROME: WERNICKE-KORSAKOFF ENCEPHALOPATHY:

Wernicke, in 1881, described a syndrome that is of relatively acute onset, occurring in alcoholics or nutritionally deficient patients and consisting of a triad: mental disturbance (confusion and drowsiness), paralysis of eye movements, and an ataxia of gait. The basic cause of the syndrome is a dietary deficiency of thiamine. As a deficiency of thiamine and of the other B-complex vitamins also results in a peripheral neuropathy, symptoms relevant to this degeneration of peripheral nerves often will be present as an associated finding. The basic pathological process consists of a necrosis of neural parenchyma and a prominence of blood vessels due to a proliferation of adventitial and endothelial cells. Petechial hemorrhages also occur about these vessels. The pathological findings involve the gray matter surrounding the third ventricle, aqueduct and the fourth ventricle. Lesions in general are usually most prominent in the mammillary bodies and the medial thalamic areas. Table 30-2 correlates the symptoms/signs with lesion location

The Memory Disturbance: As drowsiness clears it will often be noted that a severe deficit in recent memory is present, particularly if the patient has delayed seeking medical diagnosis and treatment. The patient will be unable to learn new material. He will have little memory of events surrounding his illness but will have little difficulty recalling events in the distant past. The patient may demonstrate confabulation supplying imaginary answers for questions concerning the recent past and for questions involving new material he has been requested to learn by the examiner. A significant disorientation for time is usually present. *The memory disturbance involves both retrograde amnesia (events prior to the illness) and anterograde amnesia (events since the onset of the illness).* The deficit in memory for recent events may be transient, clearing with continued treatment, or may be more persistent. The persistence of these disorders of recent memory and of the state of confusion as a chronic phenomenon is referred to as Korsakoff's psychosis. In the studies of Victor et al, pathological examination of the brain in these latter cases revealed persistent lesions in the dorsal medial and anterior nuclei of the thalamus in contrast to cases of Wernicke's encephalopathy without the persistent memory deficits. The following case history illustrates the problem of Wernicke's encephalopathy.

Case 30-1. Patient of Doctor John Sullivan and Doctor John Hills): This 62-year-old, white, right-handed stonecutter had been a known heavy alcoholic 6-8 week spree drinker for many years. Two years previously, the patient had been admitted to the Boston City Hospital because of delirium tremens (tremor and visual hallucinations). Two months prior to admission shortly following the death of a brother-in-law, the patient began his most recent drinking spree. Apparently, he had drifted aimlessly for 5 weeks with no definite food intake for a month. He unaccountably found himself in Florida, not knowing where he was and why he was there. The patient was brought back by his family and hospitalized at his local commu-

TABLE 30-2: WERNICKE'ENCEPHALOPATHY

SYMPTOM/SIGN	LESION LOCATION	EFFECT OF THIAMINE
Ophthalmoplegia (bilateral)	Predominantly CN VI, less of IIII	Rapid, reversal hours to days
Nystagmus	Vestibular nuclei	Clears over days
Drowsiness	Periaqueductal grey/ Periventricular diencephalon	Clears over days
Ataxia: gait &heel to shin	Anterior superior vermis cerebellum	If severe may persist as alcoholic cerebellar degeneration
Confusion/memory deficit	Dorsal medial/anterior thalamic nuclei	If persists: Korsakoff psychosis

nity hospital with diplopia, ataxia, marked impairment of memory and complaints of numbness of his fingertips and unsteadiness of gait. After beginning treatment, he was transferred to a neurological center

General physical examination: enlarged liver with the edge palpated approximately 2-1/2 finger breadths below the costal margin.

Neurological examination: *Mental status:* The patient was markedly disoriented for time and place Confabulation was also evident when it was suggested that he had recently seen various fictitious persons or was in particular locations. The patient was unable to state his age but could provide his birth date. He was confused with little insight as to his disorientation, or his condition. At times, the patient often indicated to visitors that his mother and father were still alive, though both parents had been dead for over 20 years. The patient's digit span was normal at 7 forward and 6 in reverse. The patient could name various objects correctly when these were presented to him and yet he was unable to retain any memory of which objects had been presented to him five minutes previously. He was unable to retain any information concerning a story that he had been requested to learn. Calculations reading and writing were intact. *Cranial Nerves:* There was horizontal diplopia on right lateral gaze. A minor weakness of the right lateral rectus was suspected[3]. Horizontal nystagmus was present on lateral gaze, bilaterally and vertical nystagmus on vertical gaze. *Motor System:* a minor degree of weakness was present in the distal portions of the lower extremities. There was no longer an ataxia of gait but a positive Romberg test was present. *Reflexes:* Deep tendon reflexes were absent at patellar and Achilles even with reinforcement. *Sensory System:* Pain and touch were decreased in the lower extremities below the mid calf. Vibratory sensation was absent at the toes and decreased over the tibia to a marked degree and to a lesser degree over the knees and at fingertips and wrists. Position sense was decreased at fingers and toes.

Clinical diagnosis:

1) Wernicke' encephalopathy
2) nutritional poly neuropathy

Hospital course: The patient was treated with thiamine. There was a significant improvement in extraocular functions. The patient had no diplopia after the day of admission. There was no significant change in his mental condition or peripheral neuropathy. Evaluation 3 months later indicated persistent disorientation for time and place and severe selective deficits in memory (delayed recall was still grossly defective) suggesting a residual Korsakoff psychosis.

In many cases, the state of confusion in Wernicke's encephalopathy is preceded by or accompanied by a period of delirium tremens indicating alcohol withdrawal. The use of intravenous glucose feedings without supplemental intravenous thiamine during such a withdrawal state may actually increase the requirements for thiamine, thus exacerbating the thiamine deficiency state. For this reason, all patients under treatment for alcohol withdrawal (or admitted to the hospital with a recent past history of alcoholism) should be treated with high dosage B vitamin therapy as well, on the presumption that they are candidates for nutritional deficiency.

In general, as we have indicated, the majority of patients with Wernicke's encephalopathy progress to a more persistent memory disturbance. Victor and Adams reported that 75 percent of their 86 cases progressed to a permanent amnestic confabulatory syndrome. The Korsakoff syndrome with its particular deficits in memory may also occur in other disease states involving the diencephalon:

(1) Tumors involving the posterior but not the anterior hypothalamus affect recent memory.

(2) Infarcts of the medial or anterior but not the posterior thalamic areas may also produce defects in recent memory. Refer to case 30-7 and Fig. 30-10 below. In the study of von Cramon et al (1985) a combined lesion of both the mamillothalamic tract and the ventral portion of the lamina medullaris interna were

most effective in producing amnesia. (See also Graff-Radford, et al, 1990 and Tatemichi, et al, 1992)

(3) Lesions of the fornix may also be associated with significant problems in memory recording. Such damage is likely to occur with colloid cysts or with the surgical procedure necessary to remove this potentially life-threatening nonmalignant tumor (see–Fig 27-11). The effects are most prominent if bilateral but may also occur with unilateral left-sided damage. Recall that the fornix is the major outflow pathway from the hippocampus. Defects in recent memory have also been reported in tumors involving the posterior or anterior portion of the corpus callosum.

(4) Lesions of the basal forebrain as in anterior communicating artery rupture. (Irle et al, 1992 Morris et al 1992) may produce persistent anterograde and retrograde amnesia.

BILATERAL LESIONS OF HIPPOCAMPUS (BILATERAL MESIAL TEMPORAL LOBE LESIONS):

The anatomy of the hippocampus and its connections has been considered in detail in chapter 22, and should be reviewed at this time.

Bilateral Ablation: Scoville and Milner (1957) were the first to observe the effects of bilateral mesial temporal lesions following bilateral ablation of the anterior two-thirds of the hippocampus and the parahippocampal gyrus with removal of the uncus and amygdala (Corkin et al, 1997). This surgical procedure had been performed for treatment of temporal lobe epilepsy in a patient who had bilateral temporal lobe epileptic spike foci. Following surgery, a gross loss of the ability to retain current experiences and to learn new material was noted, in addition to a significant retrograde amnesia. Remote events were well recalled. It should be noted that a similar defect might follow unilateral ablation of the temporal lobe structures if disease were present in the contralateral temporal lobe (Penfield and Milner (1958). These observations stimulated considerable clinical and experimental investigation. Extensive studies in the monkey by Squire and Zola-Morgan (1991) have now clarified the relative roles of these structures.

Essentially, monkeys with selective bilateral lesions of the hippocampus are impaired in memory tasks that involve the ability to acquire new information (declarative memory) but are not impaired in their capacity for skill and habit learning (that is, non-declarative memory). The type of task employed by Squire and Zola-Morgan is the delayed nonmatching to sample: A single object is presented; after a delay, two objects are presented - the original object and a novel object. The animal is rewarded for choosing the novel object and rapidly learns to select the novel object. Monkeys with selective bilateral lesions of hippocampus, parahippocampal and entorhinal cortex were even more impaired than monkeys with a selective hippocampal lesion. The entorhinal/parahippocampal areas receive input from all of the higher sensory association neocortical areas and then project via the perforant and alvear pathways to the hippocampal formation. There are however other inputs to the hippocampus. Monkeys with bilateral lesions of the perirhinal cortex and parahippocampal cortex sparing the hippocampus also demonstrated severe impairment on these same memory tasks. Combined bilateral lesions of hippocampus, parahippocampal gyrus and perirhinal cortex produce greater impairment of memory than the selective lesions of hippocampus and parahippocampal gyrus. Monkeys with selective bilateral lesions of entorhinal cortex demonstrated impairment but recovered when retested at 9-14 months (Leonard et al, 1995). All of these monkeys had no impairment of remote memory. Monkeys with lesions of the amygdala demonstrated a marked alteration in emotional behavior but had no impairment on memory tests (see chapter 22 and Zola-Morgan et al, 1991).

While most patients with bilateral medial temporal lesions have both retrograde and

anterior grade amnesia, several recent studies have allowed a differentiation of these two aspects of amnesia. Zola-Morgan et al, 1986, reported that a patient with selective bilateral lesions of the entire rostral caudal extent of field CA1 of the hippocampus (due to global ischemia) had enduring anterograde amnesia but minimal retrograde amnesia. Rempel-Clower et al, 1996, confirmed this in an additional group of three patients. On the other hand, Kapur et al (1992) described a patient with a closed head injury who had severe post-traumatic retrograde amnesia (extending back to childhood) but only mild patchy anterograde amnesia. On MRI scan, there was bilateral damage to anterior temporal cortex and to a lesser degree prefrontal areas. There was no damage to hippocampus, thalamus or other limbic structures of the diencephalon.

Disease involving the medial temporal areas may occur under a variety of circumstances and may result in an inability to retain current experiences and to learn new material. Material learned and already stored in long term remote memory will be intact. In the clinical discussion that will follow, we will often be considering the medial temporal areas in a more general sense. As already noted early cases of destruction of medial temporal areas were nonselective. Damage to hippocampus also included damage to amygdala and the adjacent cortex.

Bilateral Infarction - Bilateral infarction of the hippocampal areas may occur with disease of the posterior cerebral artery (Victor et al, 1961 and De Jong et al 1969). Occlusions of the posterior cerebral arteries usually reflect embolic events with the embolus originating in the heart or at a lower level in the vertebral basilar circulation. The ischemia or infarction of the mesial temporal areas may be accompanied by ischemia or infarction of the territories of the calcarine arteries. In other cases stenosis of the basilar artery may produce decreased blood flow in both posterior cerebral arteries. In still other instances, the ischemia apparently may be limited to the medial temporal area, that is, hippocampal areas, with little involvement of the occipital cortex. In these cases, transient episodes may occur and may be difficult to distinguish from the syndrome of transient global amnesia.

We should note at this point, that the posterior cerebral arteries via their penetrating branches also supply the medial diencephalic areas. Such ischemia in the posterior cerebral circulation, then, might well produce ischemia of the dorsal median nucleus, the anterior thalamic nuclei, and the mammillary bodies. Thus, in the case of persistent memory deficit following posterior cerebral artery lesions reported by Victor et al (1961), the areas of infarction involved not only the hippocampal formation and fornix but also the mammillary bodies. An example of bilateral medial thalamic lesions producing alterations in recent memory has been provided in Chapter 29.

Unilateral Infarcts: The study of Ott and Savez (1992) demonstrated the occurrence of the amnestic syndrome following infarcts within the territory of the posterior cerebral artery involving the hippocampus or the thalamus. In 85% of unilateral infarcts, the lesion was left sided.

Transient Global Amnesia Syndrome: This syndrome involves the sudden onset of a defect in memory. The memory deficit is similar to that which occurs in the amnestic confabulatory syndrome seen in Wernicke's encephalopathy. There is a significant retrograde amnesia for the events of the preceding days, weeks, and months. This retrograde amnesia slowly clears over a period of hours. The patient has a persistent amnesia for the period between the onset of the attack and the point of complete recovery. During the period of the episode, the patient is unable to learn new material, that is, the patient is unable to register new memories. Apart from this defect, the patient usually shows no other abnormality of behavior during the episodes. For sometime, a possible vascular etiology involving the posterior cerebral arteries (or basilar vertebral system) has been postulated. Whether the selective transient ischemia involves the hippocampal formation, rather than the dien-

cephalic areas remains unclear. As discussed, the hippocampus is more likely to manifest a selective vulnerability to anoxia and would be expected to show functional impairment prior to the medial thalamic areas. Mathew and Meyer (1974) demonstrated that elderly patients with transient global amnesia had one or more risk factors for vascular disease and 4-vessel angiography demonstrated significant lesions in the vertebral basilar and posterior cerebral systems. Patients with single episodes had no permanent impairment of memory. Those with recurrent episodes had some degree of permanent memory impairment, as well as mild visual spatial or visual motor dyspraxia. Several recent studies confirm the previously postulated ischemic etiology but leave undecided the location of the ischia: thalamus versus hippocampus (Goldenberg et al, 1991 Stillhard, et al, 1990 Lin et al, 1993). The majority of patients makes an apparent total recovery and do not have significant infarcts (see Melo, 1992). The following case history illustrates this syndrome. A transient disease process involving the temporal areas is suggested but not proven.

Case 30-2: This 55-year-old, right-handed, white male, college professor, awoke at 3:00 a.m. on the morning of admission in an uneasy and restless state. He was confused as to time, kept repeating himself and asking the same questions. His wife arranged for him to be seen early in the morning by his family physician who lived a short distance away. At approximately 8:00 he became lost driving a familiar route to his doctor's office and when he arrived with the assistance of his wife, he was unable to explain why he had come. He could remember no significant events from the 3-week period prior to the onset of his illness. The patient's more remote recall and other intellectual capacities remained intact.

Neurological examination: When examined in the early afternoon, findings were essentially limited to the mental status examination: the patient was beginning to regain some of his ability to retain new information he was still disoriented for the day and month. Store of information was quite intact.

The patient had marked difficulty with delayed recall. He could recall none of the 4 objects after 5 minutes. He could not remember any of the three test phrases given to him when asked about these 5 minutes later. He did recall in a vague manner that a memory test had been given him. was unable to remember his visit to his family physician earlier in the day. Digit retention, however, was relatively well -preserved; 6 forward and 5 backward. The patient had no defects in calculation. There was no evidence of a constructional apraxia. Language function was entirely intact.

Clinical diagnosis: Probable transient global amnesia

Laboratory data: EEG and CSF were all within normal limits.

The brain scan demonstrated a small area of increased uptake of radioisotope (Hg197) in the left temporal region.

Hospital course: Over the several hours following admission, the patient gradually regained his ability to retain new information and to recall the events of the preceding 3 weeks, the more remote events being recalled first. The memory for the events of the day prior to admission was regained last. This pattern is referred to as a shrinking retrograde amnesia. The specific events that occurred on the morning of admission were never recalled. The following morning delayed recall was four-out-of-four objects after 8 minutes. The patient's mental status and neurological examination were otherwise within normal limits. All brain scan findings had resolved at 5 months. No additional episodes occurred during the one-year after the acute episode.

Stimulation Of The Temporal Lobe:

Bilateral stimulation of the temporal lobe or unilateral stimulation with secondary spread to the contralateral hemisphere may occur during limited electric stimulation of the medial temporal structures during epilepsy surgery or unilateral electroshock therapy, during general stimulation of the brain (electrical shock

therapy or a spontaneous generalized convulsive seizure), or during a temporal lobe seizure. Thus, it may be demonstrated that electrical stimulation of the depths of the temporal lobe in patients susceptible to temporal lobe seizures can produce a defect in memory for recent events without disturbing the patient's ability to recall remote memories. In general, the longer the stimulation, the longer the duration of retrograde amnesia and the longer the recovery time before the new memories can be recorded. Table 30-3 summarizes the example cited by Doty, (1967)

A primary or secondarily generalized convulsive seizure is followed by a period of confusion during which the patient is confused, unable to record new information and uncertain of memories prior to the seizure. In general, on recovery from this period of confusion, the patient is amnestic for the entire period from the beginning of the seizure until the clearing of the postictal confusion. The patient usually, however, has no impairment of retrograde memories up to the point of the seizure. Thus any "aura" may be recalled. *The effects produced by electrical stimulation of the hippocampus may also occur as relatively selective ictal and postictal phenomena in a complex partial seizure originating in mesial temporal lobe structures* as illustrated in the **case history 30-3 presented on the CD ROM**. Focal temporal lobe seizure phenomena were followed by a period of impaired recent memory with an inability to record new memories.

Selective Vulnerability of the Hippocampus to Anoxia Or Hypoglycemia or Status epilepticus: As discussed in chapter 22, **transient** or permanent defects in memory may occur. The effects of repeated seizures on the hippocampus may involve more than simply the effects of hypoxia. Excessive discharge of neurons may also damage the neurons due to excitotoxic effects of the glutamate transmitter.

Toxic effects on the hippocampus: A recent accidental intoxication of nature provides additional information about selective damage to the hippocampus resulting in an amnestic syndrome. In 1987, an outbreak characterized by gastrointestinal symptoms and neurologic symptoms occurred in Canada in 107 persons who had eaten cultivated mussels from Prince Edward Island. The acute phase symptoms consisted of headaches, seizures and hemiparesis. Twenty-five percent of patients had persistent severe anterograde amnesia. PET scanning demonstrated decreased glucose metabolism in the medial temporal areas. In the four patients who died, necrosis and loss of neurons occurred predominantly in the hippocampus and amygdala, (Teitelbaum, et al, 1990). Two patients also had involvement of the dorsal medial thalamic nucleus. Not all patients with the persistent memory deficits had uncontrolled status epilepticus - which may also produce hippocampal damage. The mussels were found to be contaminated by domoic acid produced by a form of marine vegetation; Nitzchia pungens. Domoic acid has structural similarities to the natural excitatory transmitter glutamic acid and to kainic acid. Both kainic acid and domoic acid bind strongly to the glutamate receptor. Domoic acid is 30 - 100 X more potent than glutamate and 2 - 3 X more potent than kainic acid. Experimental administration of domoic acid or of kainic acid to rats produces limbic seizures, memory disorders and degeneration of the hippocampus.

TABLE 30-3: STIMULATION OF "DEEP" TEMPORAL STRUCTURES (AFTER DATA OF DOTY, 1967)

Duration of Stimulation	Length of Retrograde Amnesia	Length of Anterograde Amnesia
2 seconds	Just prior to stimulation	1-2 minutes
5 seconds	Current day	5-10 minutes
10 seconds	Previous 3 weeks	1-3 hours

Herpes Simplex Encephalitis: As discussed in chapter 27, the virus; herpes simplex type 1, the agent responsible for the common cold sore, may on occasion invade the central

nervous system *(Fig 30-1)* and produce several syndromes In addition to the more common acute generalized or focal encephalitis a third rare syndrome results from a more localized involvement of the medial temporal structures and is characterized by a subacute but progressive dementing process and temporal lobe seizures.

The disturbance of mental status is characterized by confusion and disorientation with a defect in memory for recent events and often for remote events as well. There is a marked inability to form new associations. The selectivity of the memory disturbance is less evident in these cases than in those cases of hippocampal disease previously discussed in detail.

TRAUMATIC AMNESIA:

Perhaps the most common transient impairment of memory occurs in relation to head injury. When blunt trauma to the head occurs, consciousness is lost. As the individual recovers consciousness, there is a period of confusion before a return to normal behavior. The loss of consciousness and the subsequent period of confusion in such patients are often referred to as concussion. Following this period of confusion, there is often a period during which behavior is otherwise normal but the ability to form new memories is defective. Examination of the patient at that time will indicate that not only is there no memory of the actual period of unconscious-ness and the following confusional state but also that there is defective memory for a period of time preceding the period of injury. The patient has then both an anterograde and retro-grade amnesia. In general, the longer the period of retrograde amnesia the more severe the head injury and in general, the longer the period of time before memory will be regained. As recovery occurs, the period of retrograde amnesia is gradually reduced. The underlying pathophysiology has been discussed previously in the section on trauma.

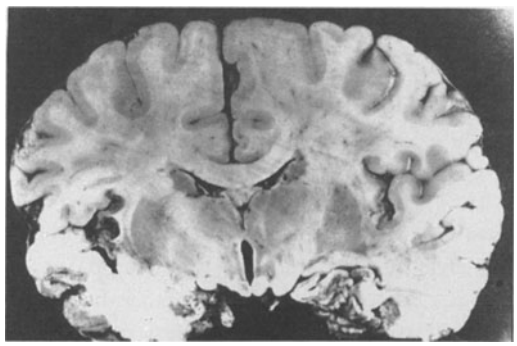

Figure 30-1. Herpes simplex encephalitis. Predominant involvement of medial and inferior temporal structures (and of insula) by an acute necrotic process is evident, although a generalized encephalitis was also present. Same case as Figure 27-26. (Courtesy of Dr. John Hills)

PROGRESSIVE DEMENTING PROCESSES

Introduction

As already defined dementia refers to a progressive impairment of previously intact mental faculties. In general, in the most common type, Alzheimer's disease, the loss involves initially and most severely recent memory and the ability to learn and retain new memories. To some extent, particularly as time passes, other areas of mental capability are also affected: remote memory, abstract reasoning, insight, and arithmetic abilities, language function, personality mood and social behavior. In other types, such as the "frontal temporal dementias", personality and behavior are involved earlier than memory .In still other types, Lewy body dementia, motor function is early involved followed by memory. In general, these processes involve the older adult population. However, certain rare disorders producing a progressive dementia affect infants, children and adolescents and the young or middle-aged adult. Some of these pediatric disorders reflect known or suspected inborn and genetic errors of metabolism: aminoaciduria, lipidosis, galactosemia, Hurler's disease (accumulation of mucopolysaccharides), and leukodystrophies. Other disorders are placed in the degenerative category because in general the etiology remains unknown; e.g., spongy degeneration. A detailed consideration of these various early

onset problems is beyond the scope of this text. Dementia is a major medical problem because of its high frequency in the elderly and because of the significant aging of the population. Life span has been significantly extended but the capacity to prevent the dementing disorders is limited. The prevalence of dementia and of Alzheimer's disease in the general population is presented in Table 30-4.

The frequency of various types of dementia is indicated in Table 30-5.

At one point the dementias were classified as cortical (Alzheimer's was cited as the most common example), or subcortical (Parkinson's, Huntington's, PSP, were cited as subcortical examples). However, degeneration of the subcortical basal forebrain nucleus of Meynert is prominent in Alzheimer's disease and cortical pathology or indirect cortical effects can be demonstrated in most of the so-called subcortical models. Although rare thalamic dementia may occur. An example is provided in case history 30-7 below.

ALZHEIMER'S DISEASE:

The most common cause of a progressive impairment of mental faculties in the older adult population is the degenerative disease known as presenile or senile dementia (Alzheimer's disease). Whether the process is called presenile or senile is arbitrary, based on the age of the patient. When the process begins before the age of 65 years, the designation presenile is used; when the process begins after the age of 65 years, the designation senile is employed. The basic pathological process (Perl, 2000) is, however, the same. Grossly *(Fig. 30-2)*, there is an atrophy of cerebral cortex, involving primarily in a diffuse manner the frontal and temporal areas but sparing the motor cortex, sensory and visual areas. In some cases, (more often presenile) involvement of the parietal association areas is evident as well. There is a thinning of gyri and widening of sulci. There is usually a secondary dilatation of the lateral ventricles. These findings in patients with senile dementia overlap with the patients in the same age group without dementia. In presenile patients, there is less overlap with non-demented patients and the atrophy and the microscopic changes discussed below are also more widespread. There is no one to one relationship of the degree of neocortical atrophy with the severity of the dementia. These overall findings are reflected in the neuroimaging studies. Thus, patients with a significant degree of dementia may manifest only a minimal degree of neocortical atrophy as noted on the CT or MRI scan. On the other hand, it is not unusual to find elderly patients with a significant degree of neocortical atrophy on such radiological studies that demonstrate relatively little actual cognitive impairment. There is, however a significant correlation in Alzheimer's disease between the degree of atrophy of the hippocampus and the presence of dementia. This hippocampal atrophy is evident on the CT scan but is best seen in MRI studies that utilize measurements of hippocampal volume *(Fig.30-3)*. **It is evident then that the earliest changes occur in the hippocampus and entorhinal cortex.**

The microscopic changes probably have a higher correlation with Alzheimer's disease than the gross changes in neocortex. These microscopic changes may be outlined as follows:

TABLE 30-4: PREVALENCE OF DEMENTIA AND ALZHEIMER'S DISEASE

AGE RANGE YEARS	60-64	65-69	70-74	75-79	80-84	85-93 ****
Overall all Types/100**	0.4	0.9	1.8	3.6	10.5	23.8
Alzheimer's Disease/100***	0.3*		3.2*		10.8*	

* For Alzheimer's disease, age ranges are 60-69,70-79,80-89

** Derived from Bachman et al, 1992 (Framingham). *** Derived from Rocca et al (1991)

**** Skoog et al, 1993, in 494patients at age 85 (Sweden) overall prevalence 29.8%: Severe 11%, moderate, 10%, mild 8%.

TABLE 30-5: CAUSES OF DEMENTIA

NEUROPATHOLOGICAL & CLINICAL SYNDROME*	PERCENTAGE OF TOTAL
Alzheimer's disease	55%
Dementia with Lewy bodies	15-20%
Multi-infarct and other vascular dementia**	15%
Combined multi-infarct/vascular plus Alzheimer's disease	12%
Other degenerative causes***	<3-5%

* Derived from Tomlinson et al, 1970, McKeith & Burn, 2000 and other sources

** Vascular dementia includes a variety of syndromes: 1.A single infarct in areas critical for memory. 2) Infarcts (single or multiple) in which total volume of cortex destroyed is >100ml. 3) Small vessel disease producing multiple lacunar infarcts) senile leukoencephalopathy: involving periventricular white matter in association with hypertension (Roman et al, 1993)

*** Frontal-temporal dementia including Pick's disease, Huntington's disease, Progressive Supranuclear Palsy (PSP)

1. **Loss of neurons in the cerebral cortex:** The large pyramidal cells of the frontal, temporal and parietal association areas neocortex and particularly the hippocampal and related medial temporal areas. Some loss of neurons occurs in all normal aging individuals but the degree in Alzheimer's is markedly greater.

2. **Loss of neurons** in certain subcortical nuclei that project to cerebral cortex: The basal forebrain nucleus of Meynert (cholinergic), the locus ceruleus (nonadrenergic), and the amygdala.

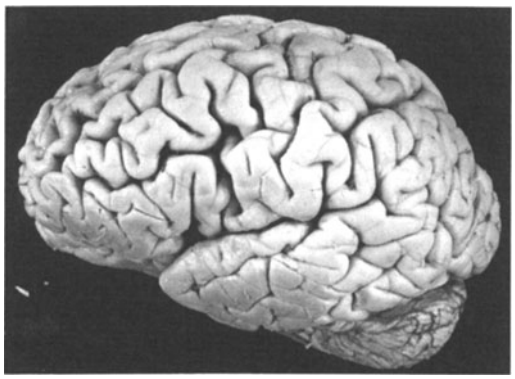

Figure30-2. Cortical atrophy as found in presenile and senile dementia of Alzheimer type. There is widening of sulci and narrowing of the gyri, particularly in frontal areas.

3. **Loss of dendritic spines** and branches affects the pyramidal neurons of the temporal and frontal cortex and the limbic cortex. Normal aging individuals actually have an increase in dendritic trees until the 80s and 90s are attained.

4. **Neurofibrillary tangles,** develop within the cytoplasm of the surviving large pyramidal neurons of these neocortical areas and the hippocampus *(Fig. 30-4, 30-5)*. These tangles are composed of the spiral (helical) winding of paired protein filaments probably derived from the protein skeleton of the cytoplasm. They contain tau proteins, a normal constituent of microtubules. Normally these tau proteins are highly soluble .In Alzheimer's disease, the tau protein found in the paired helical filaments is hyper phosphorylated and highly insoluble. These insoluble tau aggregates in the tangles are usually complexed with another protein ubiquitin. The anterior frontal, temporal neocortex, and particularly the medial temporal area (hippocampus and entorhinal cortex) are primarily affected. The amygdala, basal forebrain, cholinergic nuclei, thalamus, substantia nigra and locus ceruleus are also affected. Betz cells of the motor cortex and the Purkinje cells of the cerebellum are resistant to the degeneration. Neurofibrillary tangles also occur in a number of other CNS diseases that have been grouped together as tauopathies. It is likely that the change in tau protein represents a response of neurons to a variety of pathological insults of a genetic and non-genetic nature. These include such entities as Down's syndrome, post encephalitic Parkinson's disease, amyotrophic lateral sclerosis/Parkinson-dementia complex observed primarily on Guam, progressive supranuclear palsy, corticobasal degeneration, and hereditary frontal temporal dementia (linked to chromosome 17), as well as dementia associated with repeated head trauma in boxers.

Some neurofibrillary tangles will be found in the brain of intellectually normal individuals primarily in the anterior medial temporal areas,

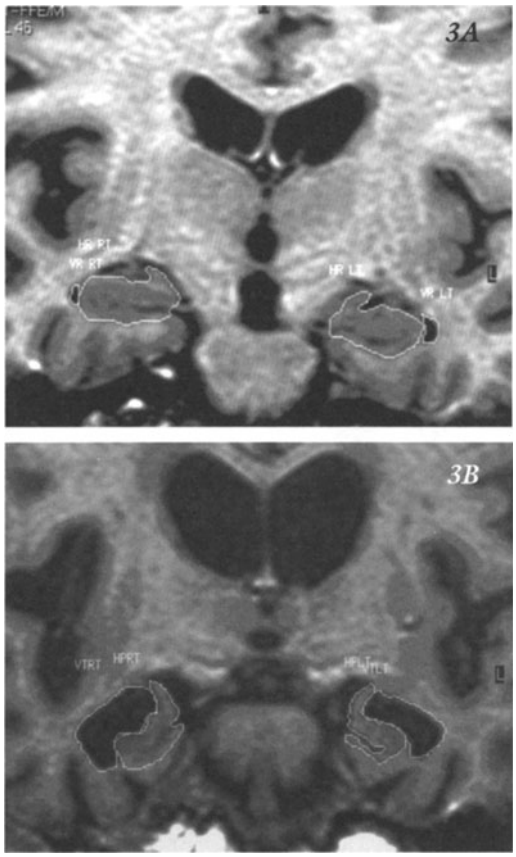

Figure 30-3. Atrophy of the hippocampus in Alzheimer's disease. MRI: area of hippocampus circled for quantitative analysis. A) Normal hippocampus in a 92-year-old patient with Parkinson's disease but normal cognitive function. B) Severe atrophy of hippocampus in a 72-year-old patient with well developed Alzheimer's disease. Neocortical atrophy is also present. (Courtesy of Dr. Daniel Sax).

but in comparatively small numbers. In the studies of Tomlinson, 5% of normal patients of 40 years had some minor involvement. By the seventh decade, 50% of patients had some involvement and all 90-year-old patients were affected to some degree. In Alzheimer's disease not only is the anteromedial temporal lobe affected to a much greater degree but also there is widespread involvement of the remainder of the hippocampus and marked involvement of the neocortex.

In some patients with clinical Alzheimer's disease, an alternate form of neuronal inclusion is found in the cortical pyramidal cells; the Lewy body composed of a-synuclein protein already discussed in relation to Parkinson's disease. These cases are labeled as the Lewy body variant of Alzheimer's disease.

What distinguishes the patient with Alzheimer's disease from the normal elderly patient and from the other tauopathies is the presence of the senile neuritic plaque to be discussed below.

5. **Dystrophic neurites** - These are altered neuronal processes axons, dendrites and/or synaptic terminals - found free in the neuropil as well as surrounding senile plaques *(Fig. 30-4)* The study of McKee et al, 1991, noted a significant increase in these dystrophic neurites in Alzheimer's disease and a high correlation of the number of both dystrophic neurites and neurofibrillary tangles with the severity of dementia.

6. **Extracellular Plaques (senile or neuritic plaques) containing insoluble fibrils of amyloid –beta proteins** *(Fig.30-4, 30-6, 30-7)*. In Alzheimer's disease fragments of abnor-

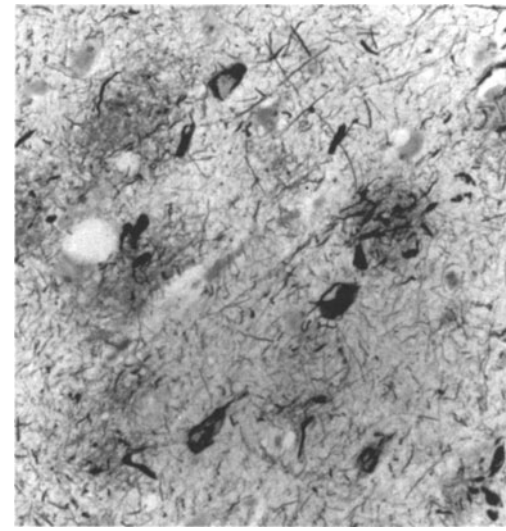

Figure 30-4. Alzheimer's Disease: Microscopic Features: This 87-year-old female had a 7 year history of a progressive dementia. This 100 x magnification section of the hippocampus CA-1 sector, stained with the Bielschowsky silver stain demonstrates the following features: (1) Loss of neurons, (2) argyrophilic neurofibrillary tangles in surviving pyramidal cells, (3) senile plaques containing fragments of silver staining neuronal and glial processes, (4) dystrophic neurites, silver staining processes surrounding the plaques (Courtesy Dr. Tom Smith).

mal appearing neuronal processes (axons and dendrites) surround the amyloid core of these plaques. There is also evidence of surrounding altered astrocytes and microglia. The plaques have a predilection for the frontal temporal and parietal association neocortex and particularly accumulate in the medial temporal areas. A "diffuse" deposit of amyloid in the neuropil, in a non-fibrillar form and without the altered glia and without the surrounding dystrophic neurites may occur in otherwise normal individuals. Similar amyloid may also accumulate in the walls of cerebral blood vessels.

The primary constituent of the amyloid core of the plaque is the B (beta) amyloid peptide of 28-43 amino acids. This peptide is generated by proteolytic cleavage of a larger transmembrane glycoprotein containing 695, 751 or 770 amino-acid residues: the amyloid precursor protein (APP). This cleavage is mediated by a series of proteolytic enzymes alpha, beta and gamma secretase. The B. amyloid in the plaque is the internal fragment of the amyloid precursor protein. Selkoe (2001) provides additional discussion of the mechanisms of cleavage.

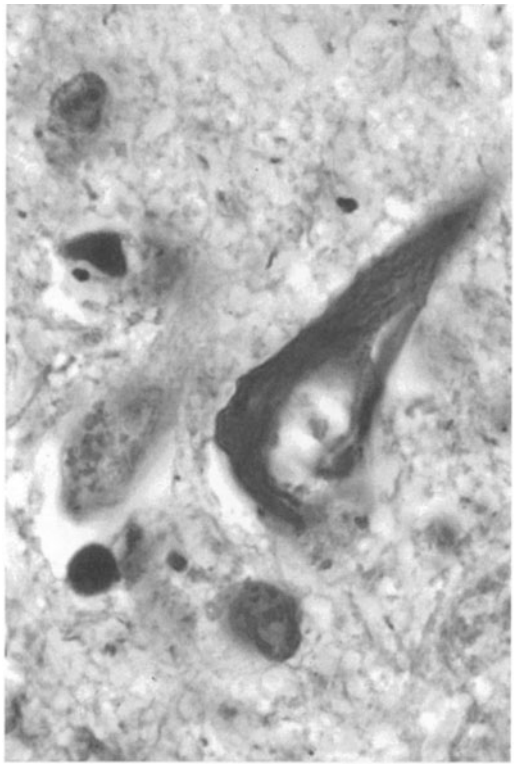

Figure 30-5. Neurfibrillary tangles in pyramidal neurons of the hippocampus. Bielschowsky silver stain. 100X magnification. (Courtesy of Dr. Thomas Smith)

A secondary area of controversy involves the relationship between the B.amyloid (and the senile plaque) and the neurofibrillary degenerative changes in the neurons and the loss of neurons. One hypothesis suggests that the local microglial activation, reactive astrocytosis and cytokine release surrounding the plaque may produce a cascade of effects that damage the neuron. An alternative hypothesis is based on the demonstration by Yankner and Mesulam, (1991) of a direct toxic effect when B.amyloid is added to tissue cultures of mature neurons. In contrast, a neurotrophic effect is evident when B.amyloid is added to a tissue culture of immature neurons. (For a review of the controversy surrounding these studies and the studies of the effects of direct injection of B.amyloid into the brain, see Marx, 1992). That there is some relationship of the senile plaques to the total process is evident, from several standpoints.

a. The plaques tend to be concentrated in those areas with severe neuronal loss and with a high density of neurofibrillary changes.

b. The relationship of Alzheimer's disease to Down's syndrome. Patients with Down's syndrome have trisomy 21. The gene for the amyloid precursor protein localizes to chromosome 21. Patients with Down's syndrome who have in a sense a triple dose of this chromosome develop a severe dementia once they reach age 40-50 (almost 100% after age 50). The dementia from a clinical and neuropathologic standpoint is identical to Alzheimer's disease. Moreover, patients with Down's syndrome dying in their teens, 20s or 30s before clinical dementia has developed will demonstrate a significant accumulation of plaques and changes surrounding the plaque prior to the development of neurofibrillary changes. Thus, the plaques may be the earliest change.

c. In some families with hereditary

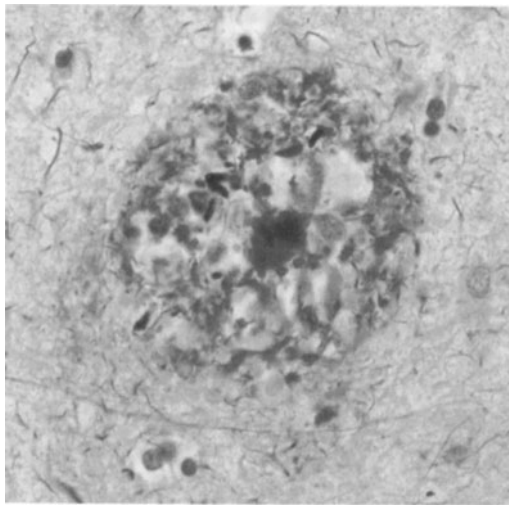

Figure 30-6. Senile plaque. Silver stain 100x magnification. Courtesy of Dr. Thomas Smith).

Alzheimer's disease of relatively early onset - a linkage to chromosome 21 could be demonstrated. In many of these families, missense mutations in the amyloid protein precursor have been demonstrated. These tend to cluster at the beta secretase cleavage site, others occur just after the gamma secretase cleavage site. All of these various mutations would result in enhanced production of increased amounts of beta amyloid. However, other familial cases have localized to chromosomes 14 or 1. In both of these latter sites, there has been localization to mutations in presenilin 1 or 2. These are membrane proteins that apparently regulate gamma secretase activity. Other late onset familial cases localize to chromosome 19. Other familial cases "The Volga Germans" localize to none of these chromosomes. The monograph of Pollen (1993) provides a review of the search for the genetic basis of the disease.

Late onset cases: All of these various mutations do not explain the majority of late onset non-familial Alzheimer's disease cases. Chromosome 19 however does provide a locus for the apolipoprotein E (ApoE) gene. Three variants (alleles) are found in the general population: E2, E3 and E 4.The E3 allele is the most common with a frequency of 0.73 .E4 has a frequency of 0.14. In families with late onset Alzheimer's disease, and individuals with late onset disease, the frequency of the E4 allele is increased to 0.40. Inheritance of one or two alleles of the E4 variant increases the density of senile plaques, increases the risk and lowers the age of onset of the late onset disease. Patients with two E4 alleles had an average age of onset 68 years; with one E 4 allele; 79 years and with no E4 allele, 84 years. By age 80, over 90% of patients with two E 4 alleles developed Alzheimer's disease, whereas only 50% of patients with no E 4 allele developed the disease by this age. ApoE 4 is a risk factor but not an invariant cause of late onset Alzheimer's disease. The E-2 variant may provide some protection from the disease. As regards the mechanism, this is not entirely clear. High concentrations of Apo E are found in liver and brain. with production in brain by glial cells. In the Alzheimer brain, ApoE has been localized to the senile plaque and to neurons containing neurofibrillary tangles. The Beta amyloid peptide binds more rapidly to

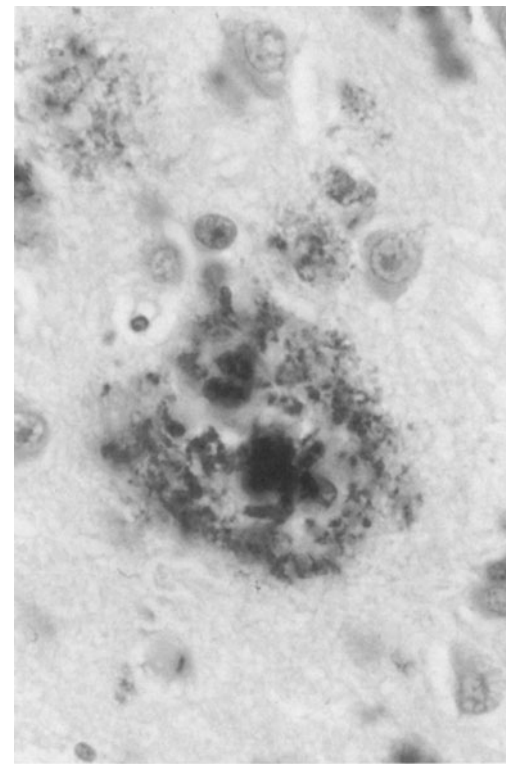

Figure 30-7. Senile plaque. Immunologic stain for beta amyloid. 100 x magnification. (Courtesy of Dr. Thomas Smith).

the E 4 form than to the E 3 form .In contrast the E 3 form binds to tau protein forming a stable molecular structure, whereas the E 4 form does not bind to the tau protein. Additional discussion of this topic will be found in Strittmatter et al (1993), Sanders et al (1993) and Corder et al (1993). Additional discussion of the molecular biology will be found in Selkoe (2001).

Clinical findings and course: The clinical symptomatology in Alzheimer's disease relates to a progressive impairment of mental faculties, usually beginning with recent (retentive) memory. Initially, the social graces, remote memory and rational reasoning capacities are well preserved. As the disease progresses, these aspects of mental function are also affected. In general, during the early stages, focal motor findings do not develop, deep tendon reflexes remain symmetrical and plantar responses are flexor. It is not unusual to have a significant degree of nominal aphasia present as the memory impairment becomes more severe. (The patient is unable to recall the names of objects.) Apraxias are also not unusual in these cases. As the disease progresses a release of a grasp reflex is also often noted. In late stages, frontal lobe gait apraxia becomes prominent and eventually, bilateral Babinski signs emerge. Eventually, the patient becomes bed ridden and unable to care for daily needs. A terminal state of paraplegia in flexion or a fetal position may be the final posture. Not all cases have the same initial appearance and not all have the same rate of progression (see Mayeau, 1985). In some cases, focal aphasia with apparent focal atrophy may be noted as an early presentation (Mesulam, 1982) but these cases are more likely to fall into the diagnostic category of frontal temporal dementia. In a considerable percentage of patients late in the disease course, myoclonus or generalized seizures or partial seizures may develop and account along with post infarct seizures for a significant increase in the frequency of seizure disorders in the elderly. Criteria for the clinical diagnosis of Alzheimer's disease have been outlined in the report of an N.I.H. work group (McKhann, et al, 1984). See also Markesbery (1992), Katzman (1993).

The following case history presents an example of presenile dementia.

Case 30-4: This 64 year old right handed white male formerly an administrative assistant for the veteran's administration and newspaper distributor was evaluated for progressive impairment of recent memory of 10 year's duration. At age 60, delayed recall was limited to 0/4 and there was minor time disorientation. During last year there were now personality changes and word finding difficulties. Family history was negative.

Neurological examination: *Mental status:* The mini mental status exam indicated a total score of 19 out of 30. He had particular problems in time orientation. He was able to do the immediate recitation of three objects and of a test phrase but could remember none of these on a delayed recall test. He also had difficulty copying a test figure. The patient was often tangential in his answers and demonstrated inappropriate joking. *Motor system:* premotor / frontal lobe functions were abnormal with a release of the instinctive grasp reflex, and impairment of motor sequences.

Clinical diagnosis: Alzheimer's disease

Laboratory data: All studies were normal except a CT scan demonstrated significant dilatation of the temporal horns suggesting hippocampal atrophy, in addition to a general increase in lateral ventricular size with blunting of the angles of the frontal horns. A SPECT scan demonstrated slight decrease in perfusion in the left parietal region.

Subsequent course: After 10 weeks of treatment with 5mg per day of donepezil (Aricept) a centrally acting acetylcholinesterase inhibitor and high dosage of vitamin E (a possible antioxidant), the test score had increased to 25 out of 30 with particular improvement in the delayed recall section of the exam. There was however no change in personality. Administration of the acetylcholinesterase inhibitor temporarily improved memory function for approximately 18 months. However by age 67, behavioral disturbance (agitation,

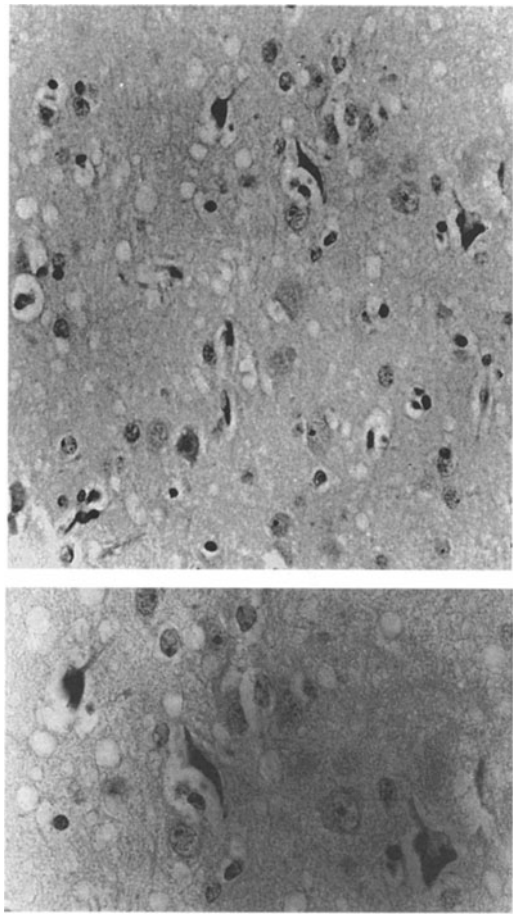

Figure 30-8 Creutzfeldt-Jakob Disease: Histological features: (A) low power H&E - approx. 40x (B) high power H&E - approx.150x. Diffuse micro vacuolization of the neuropil and neuronal cell bodies is present in this biopsy of frontal lobe. This 45-year--old female presented in November 1992 with a 3-4 week history of progressive ataxia and mental deterioration. EEG evolved into the characteristic periodic pattern. Patient expired after a total course of approximately 5 weeks. (Courtesy of Dr. Tom Mullins and Dr. Tom Smith)

aggression nocturnal wandering and sexual disinhibition) and urinary incontinence were becoming major problems. He could no longer be managed in his home and day care setting despite the use of haloperidol and he was placed in a nursing home At age 69, he was now described as relatively nonfluent, and very confused and restricted to a wheel chair. He was "stiff and afraid" when requested to walk.

The use of the donepezil has been estimated to postpone nursing home placement by approximately 15 months. The rational for the use of acetylcholinesterase inhibitors is based on the demonstration by Drachman and Leavitt (1974) that administration of scopolamine, an anticholinergic drug that crosses the blood brain barrier, would produce a transient syndrome similar in many respects to the memory and cognitive changes of Alzheimer's disease. Subsequent studies demonstrated a marked loss of neurons in the basal forebrain nucleus of Meynert, a major source of cholinergic fibers to the cerebral cortex. (Whitehouse et al 1981 Rogers et al, 1985 editorial of Growden 1992). However, a simplistic cholinergic hypothesis is insufficient to explain all of the features of Alzheimer's disease. Administration of acetylcholine esterase inhibitors in mild cases (mini mental status score of 10-25) has only a limited value as in case 30-4. Other neuronal systems are involved (noradrenergic synapses are also involved. The hippocampal system is severely involved).

The **Evaluation of the Patient with Alzheimer's disease**: The primary purpose of a complete evaluation in these cases is to rule out the treatable causes of dementia. In addition, several less frequent causes of dementia must be differentiated from Alzheimer's disease. The treatable causes of dementia are outlined in table 30-6. The usual screening tests are the following: TSH, B12, and folate, RPR or VDRL and CT scan. Other causes of progressive dementia are outlined in table 30-7.

Case 30-7: (Patient of Dr. Thomas Mullins). This 74-year-old right-handed widow presented to the emergency room at St Vincent hospital on 2-19-02 with an 8-10 week history of worsening memory problems. In December 2001, accompanied by her boyfriend she made her annual trip to Florida. Although she had been in her usual state of independent living prior to her departure, she was found to have serious problems with memory on arrival. She was unaware as to where she was. In a telephone conversation with her daughter, "she was talking non-

TABLE 30-6: TREATABLE AND RELATED CAUSES OF DEMENTIA

CATEGORY	SPECIFIC ETIOLOGY	TEST
Infections	-Tertiary syphilis (general paresis)* -AIDS dementia	-RPR, or specific FTA or CSF VDRL -If indicated HIV
Nutritional	B12, thiamin, niacin	B12 and folate levels
Intoxications	Various (Refer to chapte r27)	Toxicology screen +if suspected Pb,
Endocrine	Hypothyroid	TSH, then if +, T4, T3
Tumors	Frontal meningiomas, and gliomas**	CT or MRI scan
Post traumatic	Chronic subdural hematomas	CT scan
Hydrocephalus	NPH, etc, (ataxia>dementia)	CT scan, improve after CSF removal (30cc)
Vascular	Various types of vascular dementia	Multiple strokes+ multifocal signs, CT/MRI
Pseudodementia	Depression>dementia + variability	Trial of antidepressants
Other meningeal	Carcinomatosis of meninges	MRI, CSF cytology

* An example of general paresis case 30-5 is presented on the CD ROM **See case 30-7 and *Fig 30-10* below.

Other progressive disorders producing dementia are summarized in Table30-7.

sense". During the next 2 months, memory and word finding continued to deteriorate. She was taken to the emergency room of the local hospital in Florida where a CT scan without contrast on 02/07/02 demonstrated mild cortical atrophy but no acute process. Her son drove to Florida and found that her memory was poor and her conversation did not make sense. "My husband is in the service: my mother died last year." However she could play cards with her grand daughter. Her gait was slow and stooped. She had urinary incontinence on her way to the bathroom.

She had no history of alcoholism and took various vitamins and herbs.

Family history: her brother had died of a brain tumor of unknown type.

Neurologic examination: The positive findings were the following: *Mental status:* The patient was awake and alert. Overall Mini-Mental Status Sore was 19/30.The major problems were in orientation and in delayed recall. She was able to indicate that she was in a hospital in Massachusetts and the date was February. She registered 3 objects but could not recall any in 3 minutes. She was however able to read, name objects, follow instructions, spell "world" backwards and copy a figure. She was unable to draw a clock with the hands set at 11:10. *Motor system:* Although strength and tone were normal, her gait was broad-based and shuffling. *Reflexes:* Patellar and Achilles reflexes were absent but plantar responses were flexor.

Clinical diagnosis: 1) Subacute dementia etiology uncertain possibly of Alzheimer's or Lewy body type. Various entities such as chronic subdurals, tumor etc to be ruled out 2) Peripheral neuropathy, most likely etiology at this age diabetes mellitus.

Laboratory data: *Basic CBC and chemistries:* Normal except for an elevated fasting glucose. *CT scan (Fig 30-10):* An enhancing 2.75 cm tumor with a necrotic center was present in the thalamus at the level of the upper third ventricle. There was bilateral involvement of the anterior and medial thalamus but with no involvement of the posterior thalamus or hypothalamus. The study suggested a lymphoma or glioblastoma

Subsequent course: *Stereotaxic biopsy of the right thalamus:* Frozen section raised the question of a lymphoma or glioblastoma but special immunological stains were consistent with a glioblastoma. Necrosis and endothelial hyperplasia were present. The patient was

TABLE 30-7: OTHER PROGRESSIVE CAUSES OF DEMENTIA

DISORDER	DISTINGUISHING CLINICAL	PATHOLOGY
Diffuse Lewy* Body Disease	Parkinsonism and psychotic features with relative sparing of memory at onset	Diffuse Lewy body involvement of cortical & subcortical neurons + senile plaques
Huntington'sDisease	Chorea and personality changes at onset Autosomal dominant, high penetrance	Atrophy caudate/putamen + cortex, seen CAG trinucleotide repeats
Frontal/temporal Dementia (several types)	1) Personality changes early, memory changes late. 2) progressive nonfluent aphasia at onset. 3) semantic dementia In 40% autosomal dominant tauopathies are found linked to chromosome 17.	1) Bilateral prefrontal atrophy early, hippocampus late 2) Lobar left temporal-frontal frontal atrophy, 3) Bilateral temporal atrophy with gliosis and/or spongy changes. In some Pick's bodies.
Creutzfeldt – Jakob	Rapidly progressive dementia, myoclonus, seizures, pyramidal, basal ganglia signs (+cerebellar in 50%). Familial **and new variant (bovine) cases have a younger onset, a slower course and greater cerebellar involvement.	Transmissible spongiform encephalopathy - Prion disorder *(Fig 30-8)*. Periodic EEG complexes in sporadic *(Fig.30-9)*. In new variant, diffuse amyloid plaques +spongiform changes.

* CD ROM Case 30-6. **10-15% of Creutzfeldt Jakob cases have an autosomal dominant mutation on chromosome 20 (prion protein)

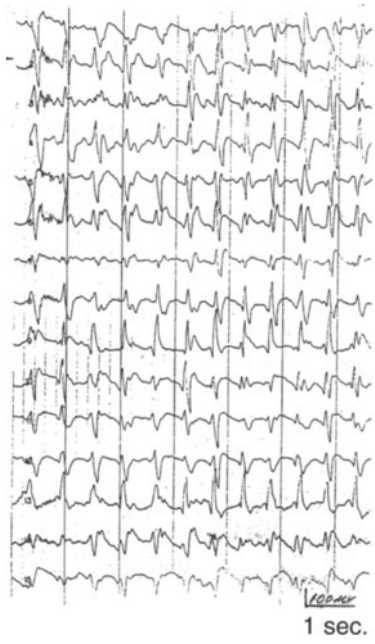

Figure 30-9 Creutzfeldt-Jakob disease: Biopsy proven spongiform encephalopathy EEG Features: Frequent periodic discharges of generalized triphasic blunt spikes are present at a late stage of the disease. This 58-year-old male was admitted on 01/18/93 with a brief subacute onset of ataxia and mild cognitive deficits and a mildly abnormal EEG. He evolved rapidly over a 4-week period, (from onset to death) both from the clinical and EEG standpoint. (Courtesy of Dr. Tom Mullins and Dr. Sandra Horowitz.)

treated with dexamethasone and radiotherapy with improvement in gait.

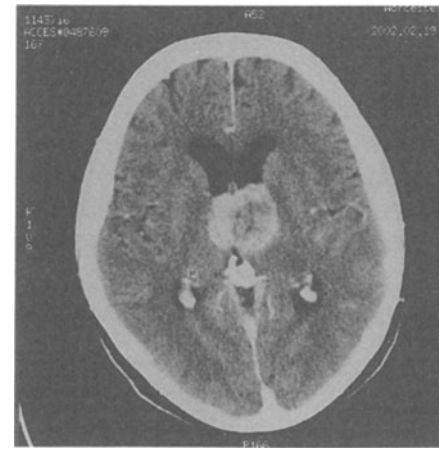

Figure 30-10: Thalamic dementia secondary to a glioblastoma. Case 30-7: CT scan with contrast. An enhancing tumor with a necrotic center involves the anterior and medial thalamus without involvement of the posterior thalamus.