THE CONTRIBUTION OF NEUROPATHOLOGIC STUDIES TO THE UNDERSTANDING OF AUTISM

Thomas L. Kemper, MD, and Margaret L. Bauman, MD

Infantile autism is a behaviorally based syndrome of unknown cause. Although some aspects of the syndrome have been noted in conditions such as phenylketonuria, neurofibromatosis, tuberous sclerosis, and the fragile X syndrome, the majority of cases are without identified cause.[24] There has been no consistently identified prenatal or perinatal risk factor.[21] Twin and sibling studies have provided evidence for a genetic liability, the mechanism of which is unknown.[13] Although early workers had suspected that it was primarily a behavioral disorder, the high incidence of epilepsy and abnormal electroencephalograms[18] have argued against this. Recently anatomic and imaging studies have provided clear evidence for abnormalities within the brain, primarily in two areas, the limbic system in the forebrain and the cerebellum and related inferior olive in the hindbrain. In this article, these anatomic changes are reviewed and their pathogeneses and relationship to the clinical features of infantile autism considered.

METHODS AND MATERIALS

We have examined a total of six brains, three from individuals in the third decade and three from individuals in the late first to early second decade. The records were reviewed by one of us (MLB), and all conformed to the current DSM-III-R criteria. Their clinical features are shown in Table 1.

All six cases were studied in whole-brain serial histologic section in comparison with identically processed age-matched and sex-matched controls.

From the Department of Neurology, Boston City Hospital (TLK); and the Children's Neurology Service, Massachusetts General Hospital (MLB); Boston, Massachusetts

Table 1. CLINICAL FEATURES

	Age in Years (Sex)					
	9 (M)	10 (F)	12 (M)	22 (M)	28 (M)	29 (M)
IQ	Severe MR	Severe MR	105	Moderate MR	Moderate MR	Severe MR
Seizures	+ +	−	−	+	+	+
Cause of Death	Dead in bed	Sepsis	Ewing's sarcoma	Drown	Sepsis	Drown

MR = Mental retardation.

Each brain was compared with its respective control with a Zeiss comparison microscope. With this microscope, selected areas of both brains could be seen side-by-side at the identical magnification. Areas of the brain that showed abnormalities in this comparison were subjected to more detailed analysis with neuronal cell counts in randomly selected fields within these areas. For the sake of simplicity, these data are reported in the tables as O for no change and + to + + + for increasing severity of cell packing density in the autistic brain. Examples of the numerical data can be found in our initial case report.[6] In each brain, comparisons were made between appropriate controls for all major subdivisions of the basal ganglia, septum, preoptic area, hypothalamus, bed nucleus of the stria terminalis, thalamus, epithalamus, subthalamus, brain stem, cerebellum, and cerebellar nuclei. For each area selected, only the central part was used to be sure that we were completely within the area of interest. We have completely surveyed the forebrain in four of these brains. The areas of consistent involvement in the forebrain are shown in Table 2. All these areas showed abnormally small, densely packed neurons (Fig. 1).

The only other consistent area of involvement was the vertical limb of the diagonal band of Broca, a nucleus adjacent to the medial septal nucleus. In the younger brains, the neurons in this nucleus were unusually large, and in the older brains, they were decreased in size and number. The only area of abnormality noted in the cerebral cortex was that in five of the six brains the anterior cingulate cortex appeared unusually coarse and poorly laminated. In

Table 2. LIMBIC SYSTEM INVOLVEMENT

	Age in Years (Sex)			
	9 (M)	10 (F)	28 (M)	29 (M)
Hippocampus				
CA4	+ + +	+	+ +	+ + +
CA3	+ + +	+ +	+ +	+ + +
CA2	+ + +	+ +	+ + +	+ + +
CA1	+ + +	+ + +	+ + +	+ + +
Subiculum	+ +	+ + +	+ + +	+ + +
Mammilary Body	+ +	+	+	+ + +
Septum (Medial)	+ +	?	+ +	+ +
Amygdala				
Cortical nerve	+ + +	+ + +	+ + +	+ + +
Medial nerve	+ +	+ + +	+ +	+ + +
Central	+ + +	+ + +	+ +	+ + +
Medial basal	+	+ + +	+ +	0
Lateral basal nerve	+ +	+ +	+ +	0
Lateral nerve	0	0	0	0

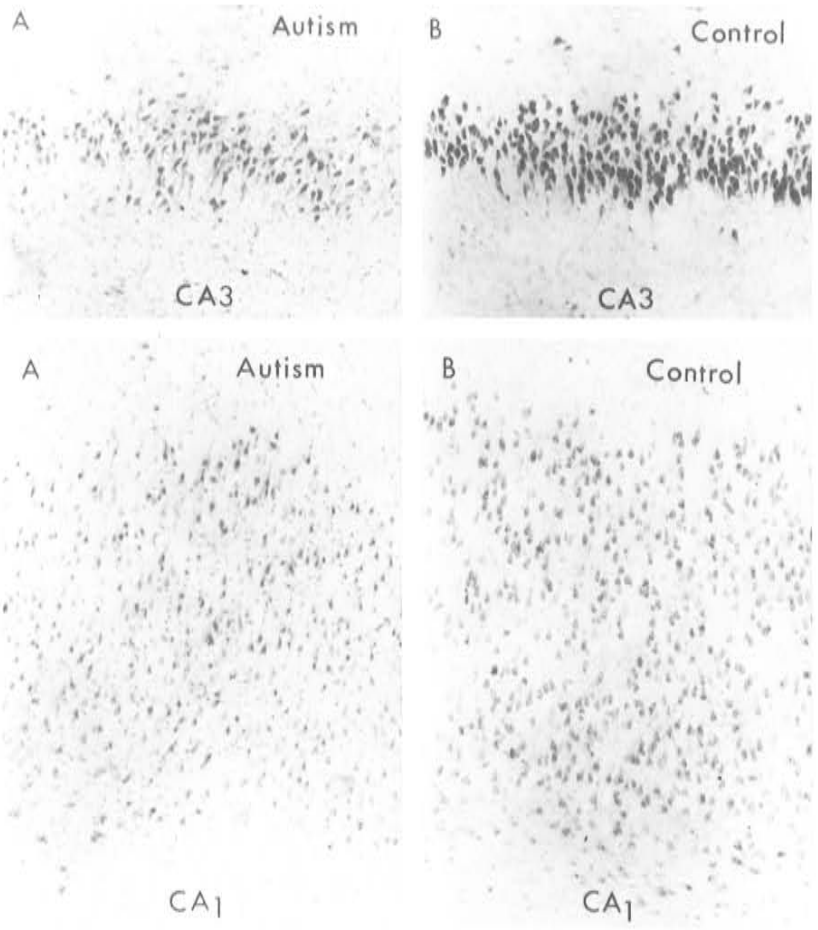

Figure 1. High power photomicrographs show unusually small, pale staining neurons in fields CA1 and CA3 of the hippocampus of a 29-year-old autistic man. (Nissl, original magnification × 63)

one brain (9-year-old boy), there was a small area of polymicrogyria in the right orbitofrontal cortex.

In the hindbrain, the consistent abnormalities were confined to the cerebellum and the related inferior olive. All brains showed a decreased number of Purkinje cells that was most marked in the posterolateral neocerebellum and adjacent archicerebellar cortex[1] (Fig. 2). The extent of this decreased neuronal density did not appear to be different in the younger and older individuals. A definite decrease in the number of granule cell neurons was found in two brains (10-year-old girl and 29-year-old man). The remaining brains showed, at most, a mild decreased number of these neurons. Definitive counts have not been made. In all brains, the inferior olivary nucleus failed to show retrograde neuronal loss. Instead, in the younger individuals, the neurons that project to the areas of decreased number of Purkinje cells were unusually large and in the older brains unusually small (Figs. 3 and 4). A similar pattern of change

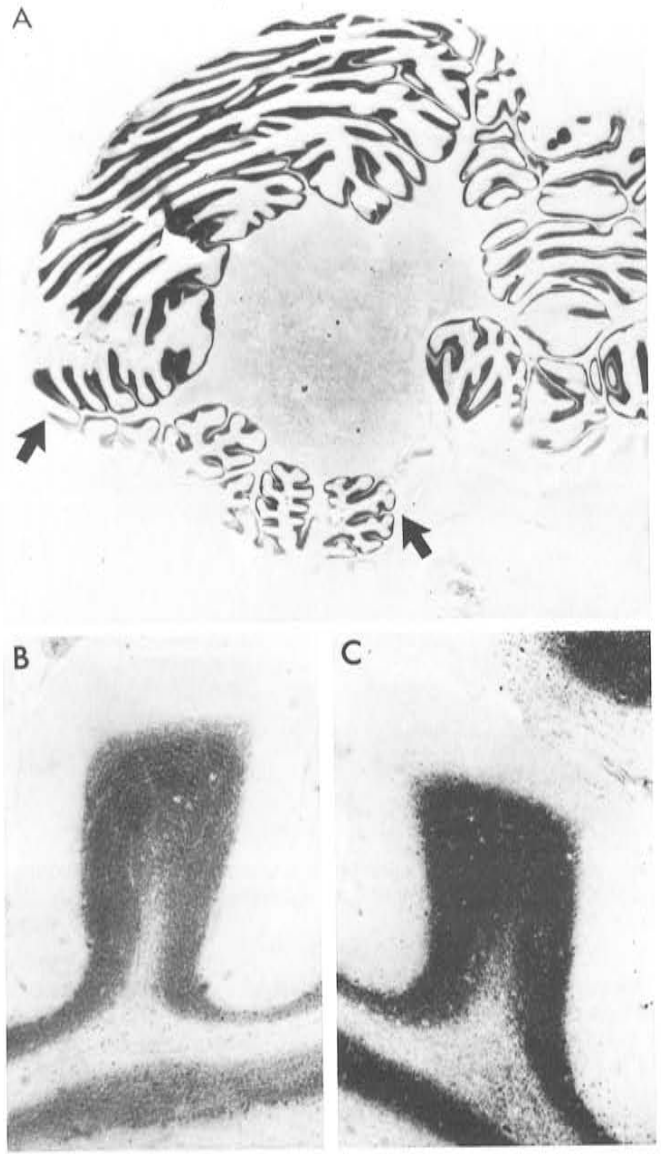

Figure 2. *A,* Low power macrophotograph of the cerebellum of a 10-year-old autistic girl. Note the atrophy of the folia in the inferolateral part of the cerebellum (between the arrows). *B,* High power microphotograph of an atrophic folia. Note loss of both Purkinje and granule cell neurons. *C,* Folia from an uninvolved part of the cerebellum. (Nissl, original magnification × 250)

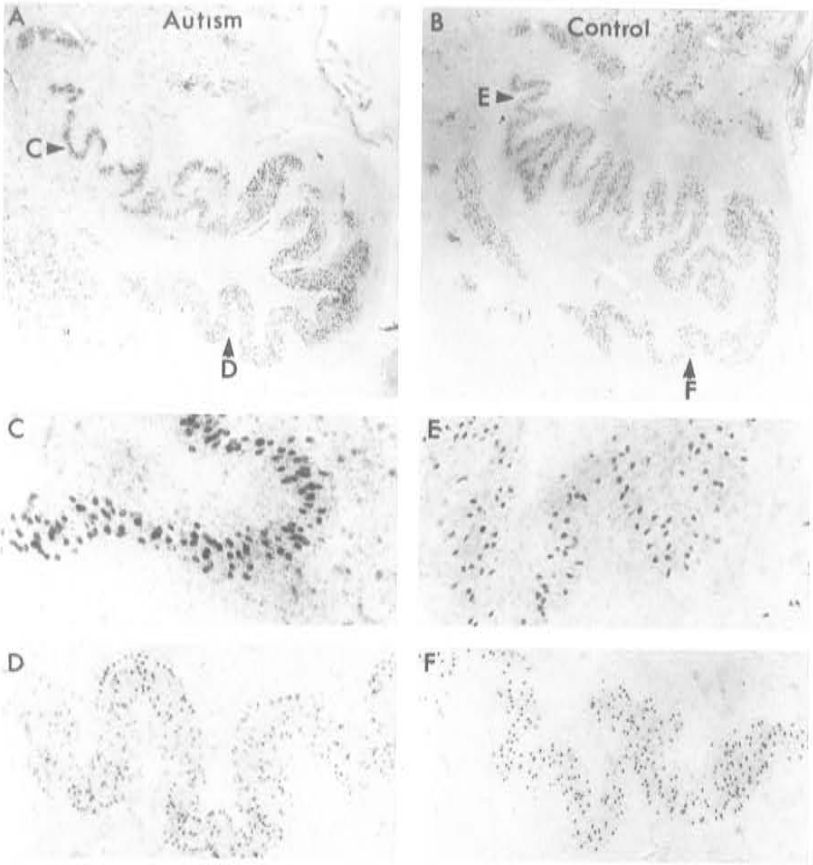

Figure 3. Photomicrographs of the inferior olive of a 10-year-old autistic girl. *A,* Note the unusually large neurons at point C and the normal neuronal size at point D. *C* and D, These neurons are shown at a higher magnification. These unusually large neurons project to the atrophic cerebellar cortex. *B, E,* and *F,* Comparable microphotographs from a control brain are shown. (*A* and *B:* Nissl, original magnification × 10; *C–F:* Nissl, original magnification × 25)

was noted in the cerebellar nuclei except that in the older individuals there was a decreased number of neurons. These changes were most marked in the roof nuclei and the fastigial, globose, and emboliform nuclei and least marked in the dentate nucleus. The extent of these cerebellar nuclear changes is shown in Table 3, and an example of abnormally large neurons in one of the younger brains is shown in Figure 5.

Individual brains showed changes in the brain stem that were not seen in the others. In one of the brains, the nucleus raphe dorsalis and nucleus locus coeruleus appeared disorganized and coarse. In another brain, there was mineralization of Purkinje cells and apparent mineralization of migrating cerebellar granule cell neurons. The latter change occurred in mirror foci in adjacent folia. Because these were inconsistent findings, their significance for autism is uncertain.

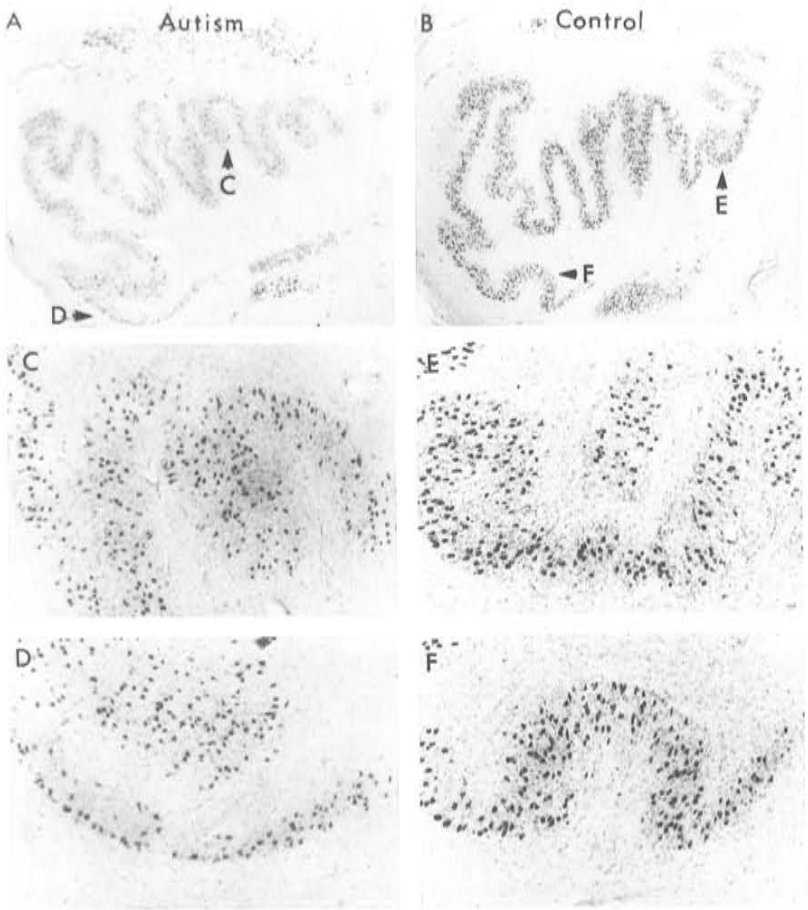

Figure 4. Photomicrographs from areas comparable to that shown in Figure 3 in the brain of a 29-year-old autistic man. The neurons in Figures 3*A* and 3*C* that were unusually large, are abnormally small in this brain (at point C in Figures 4*A* and 4*C*). (*A* and *B:* Nissl, original magnification × 10; *C–F:* Nissl, original magnification × 25)

Table 3. INVOLVEMENT OF INFERIOR OLIVE AND CEREBELLAR NUCLEI

	Age in Years (Sex)			
	9 (M)	**10 (F)**	**28 (M)**	**29 (M)**
Roof nuclei	Large cells	Large cells	Small cells Cell loss	Small cells Cell loss
Dentate nucleus	Large cells	Large cells	Normal size	Normal size
Inferior olive	Large cells	Large cells	Small cells	Small cells

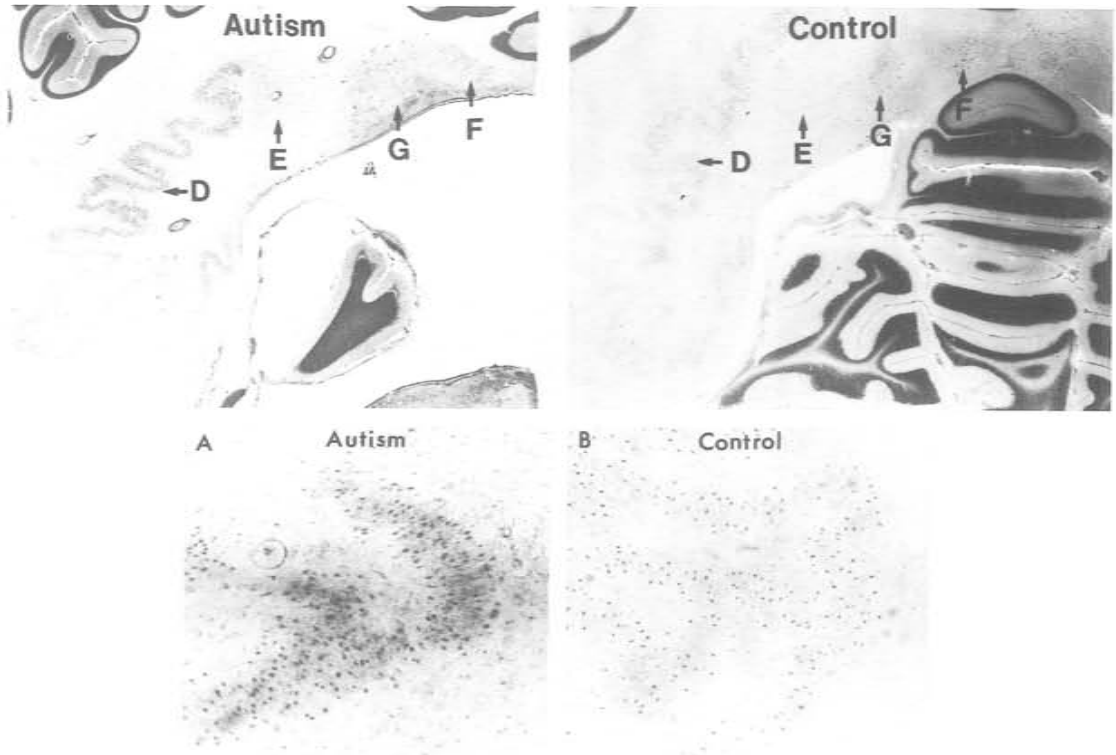

Figure 5. Photomicrographs of the cerebellar nuclei in a 10-year-old autistic girl (*left*) with an age and sex matched control (*right*). The lower power photographs (*top*) show the prominent neurons in the cerebellar nuclei in the autistic brain (Nissl, original magnification × 2). The dentate nucleus is shown at a higher magnification (*bottom*) to show more clearly the abnormally large neurons in the autistic brain (Nissl, original magnification × 25). D = Dentate nucleus, E = Emboliform nucleus, G = Globose nucleus, F = Fastigial nucleus.

DISCUSSION

Consistent neuropathologic changes were found in two anatomically distinct areas of the brain. In the forebrain, they were confined to the hippocampal formation, amygdala and closely related entorhinal cortex, mammillary body and septum, and all integral parts of the limbic system. In the hindbrain, they were confined to the cerebellar cortex and nuclei intimately related to it. The changes in the forebrain have been seen only in anatomic studies. Atrophy of the cerebellum has been reported in brain imaging studies using computed tomography scans and magnetic resonance imaging,[11] and decreased number of Purkinje cells was also noted by Ritvo et al[26] in anatomic studies.

The cerebellar changes provide the best insight into timing of the pathologic process. The absence of retrograde loss of inferior olivary neurons is a striking finding in these brains. The neurons in the inferior olive topographically project to the Purkinje cells of the cerebellum and show neuronal loss following cerebellar lesions from birth on,[8, 15] indicating a tight interrelationship between these two cell populations. In normal human development, this relationship is established after 30 weeks of gestation.[23] The abscence of retrograde cell loss in the inferior olive of the autistic brains therefore suggests that the decreased number of Purkinje cells was present before this time. Based on these observations, we have postulated a prenatal timing for the cerebellar cortical changes.[6] We further speculate that the unusually large neurons in the inferior olive and cerebellar nuclei in the younger patients and atrophy and loss of these cells in the older individuals may be related to a persistent fetal cerebellar circuit.[7] According to Flechsig,[12] the inferior cerebellar peduncle, which contains the olivocerebellar fibers, shows advanced myelination at 28 weeks of gestation. This suggests a functional projection from the inferior olive to the cerebellum at this stage of development, a stage before the development of the intimate relationship of the inferior olive to the Purkinje cells. It is presumed therefore that this projection is to the cerebellar nuclei. In the adult brain, this projection to these cerebellar nuclei is a collateral of the inferior olivary projection to the Purkinje cells.[9] Early decrease in number of its normal, eventual target, the Purkinje cells, could favor the persistence of this fetal circuit. In the brains of the younger individuals, the neurons in this hypothesized fetal circuit were unusually large, with loss and atrophy in the older individuals. We have postulated that the eventual atrophy of this circuit may be related to the lack of persistence of a circuit that was "programmed" for a fetal stage of development. These relationships are diagrammatically shown in Figure 6. The proposed unstable fetal circuit is shown with interrupted arrow, and the neurons that show atrophy and cell loss in the older individuals are underlined.

The abnormalities in the limbic forebrain are more difficult to interpret. The one change that closely follows that noted in the cerebellar circuits was noted in the vertical limb of the diagonal band of Broca. In the younger individuals, these neurons were unusually large, and in the older individuals, these same cells were small and decreased in number. By analogy with the changes in the cerebellar circuits, we suggest that a similar unstable circuit may be present in the forebrain. In the adult brain, this nucleus provides a strong, highly focused cholinergic projection to the amygdala and hippocampus. The extent of its fetal projection is unknown. It is possible that the abnormally small neurons in the hippocampal complex and the amygdala are in the fetal distribution pattern of this projection.

The pattern of abnormally small, closely packed neurons in the limbic system in the autistic brains resembles that of an earlier stage of development

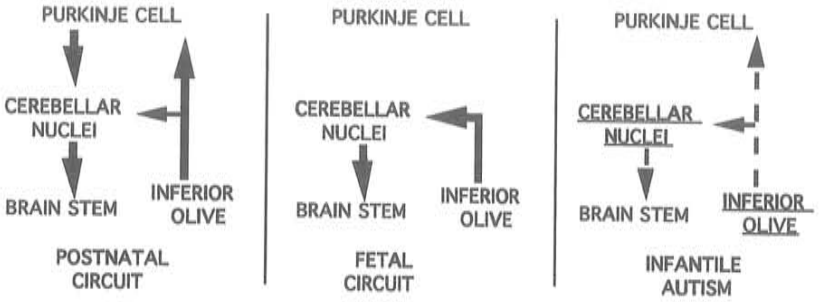

Figure 6. Hypothesized abnormal circuit in infantile autism.

and is therefore likely to represent a curtailment of normal development. Recent Golgi studies of CA1 and CA4 pyramidal cells in two brains are consistent with this interpretation.[25] These cells showed a decreased extent and complexity of their dendritic tree.

Another interesting feature of the pathologic changes in infantile autism is that they selectively involve two geographically separate areas of the brain that are strikingly different in their anatomy and function. Although they seemingly have little in common, they do share one feature that is unique to both. Both the limbic forebrain and the cerebellum have germinal zones that generate granule cell neurons over a long period of time. In the cerebellar cortex, the germinal external granule cell layer generates granule cell neurons from early in fetal life until the eleventh postnatal month.[23] In the hippocampal complex, a similar germinal zone generates granule cell neurons in the fascia dentata. Although the duration of this germinal zone in the human brain is unknown, in the rodent, these neurons are generated throughout the life span of the animal.[30] Quantitative studies have not yet been done on these cells in infantile autism.

The anatomic changes in the forebrain provide a substrate for the understanding of some of the symptoms of infantile autism. These changes are confined to tightly interrelated circuits of the limbic system, a system known to be involved in memory and emotion. Studies of human and nonhuman primates provide evidence for two memory systems in the forebrain, representational (or declarative) memory and procedural (or habit) memory.[14, 16, 19, 20, 29] Representational memory involves all sensory modalities and mediates the learning and significance of facts, episodes, and events and, as stated by Murray,[20] ". . . provide(s) us with meaning in our lives." In testing for representational memory, the subject is exposed once to a sensory stimulus followed by a single exposure to this stimulus and a novel stimulus, with a reward for the recognition of the novel stimulus. The complexity of the test can be increased by increasing the delay between the presentation of the original stimulus and the novel stimulus or increasing the number of stimuli. Habit memory is involved in skill learning and automatic connections between a stimulus and a response. In contrast to declarative memory, habit learning is not accessible to conscious recollection and is acquired by repeated presentation of the same stimuli until the task has reached criteria.

These two systems are thought to be anatomically separate. Declarative memory depends on the integrity of the hippocampus, amygdala, and areas closely related to them, with the most severe deficits noted with large lesions

that involve both the hippocampus and the amygdala together with adjacent areas. Most recently, Squire and Zola-Morgan[29] have argued for a central role for one of these adjacent areas, the entorhinal cortex. Lesions in other closely related areas have also been shown to interfere with declarative memory but to a lesser extent. These include the ventromedial prefrontal cortex, nucleus basalis of Meynert, medial and anterior thalamic nuclei, fornix, medial septal nuclei, and mammillary bodies.[19] Selective bilateral lesions of either the hippocampus or the amygdala have shown that each contributes to a different function. The hippocampus has been implicated in the spatial features of the task and the amygdala in the interrelationship of the different sensory modalities and in their interrelationship to emotional state and emotional responses. The substrate for habit memory is thought to be the striatum and cerebral cortex.

In our studies of the neuropathology of infantile autism, there is sparing of the striatum and cerebral cortex, the substrate for habit memory. In contrast, there is highly selective involvement of the hippocampal complex, amygdala, entorhinal cortex, septum, and mammillary bodies, substrates for declarative memory. The significance of these anatomic areas for memory in humans can be seen in the profound deficit in this function noted following bilateral surgical resection of the hippocampus, amygdala, and the immediately adjacent areas. The most famous of these patients, H. M., has essentially no recall of facts or events since the time of surgery, including the inability to learn new vocabulary. Thus virtually all daily experiences and events, which presumedly represent a continual exposure to novel stimuli and verbal interchanges, have left little memory trace in these patients. The effect of a congenital disturbance of this memory system is unknown. Lesions and curtailments of development in these areas, however, would be in a position to interfere with or distort the acquisition and understanding of the continuously occurring novel stimuli of daily life. Such a dysfunction could provide a substrate for the characteristic abnormalities in social interaction and language in infantile autism, functions that are derived from interaction with people. Further, there is evidence that representational memory in humans may be acquired at some time after birth, with children 45 to 81 months of age still not at adult level.[22] This could account for the frequent development of the clinical manifestations of autism during infancy and childhood.

An additional feature of these human lesion cases is the preservation of habit (procedural) memory, a memory system that appears to develop in early infancy.[22] As in these adult cases, the proposed substrate for this memory system, the striatum and the cerebral cortex, appears to be intact in the brain in infantile autism. Consistent with the preservation of this rigidly specified memory system is the frequent preoccupation with repetitive and stereotypic behavior seen in many autistic individuals. Another characteristic symptom of autism is a catastrophic reaction to change in the environment. With continued exposure to constant stimuli, such as in the appearance of the specific features of a room, the autistic individual may be able to learn its appearance with habit memory. A change of position of a piece of furniture in the room, however, may render the previously familiar room unrecognizable and therefore foreign. In addition, because habit memory is not accessible to verbal expression, the memory of the details of the room cannot be expressed verbally. The observer understands that the details are known only from the reaction to change.

Support for this proposed role of these mesial temporal limbic areas in the symptoms of infantile autism is provided by experimental studies in monkeys.[2, 3, 17] In these studies, the amygdala and hippocampus were bilaterally resected,

with one side lesioned at 1 week and the other at 3 weeks after birth. Memory function and behavioral development were assessed at 2 to 3 months, 6 months, and beyond. When first tested, control monkeys showed acquisition of habit memory at the adult level. An adult pattern of representational memory was found at 2 years of age. The latter was severely impaired in the lesioned monkeys, as was their emotional and social development. At 2 to 3 months of age, the lesioned monkeys, when placed in a novel play cage, showed more temper tantrums and more passive behavior and manipulated objects less than controls. At 6 months of age, they showed complete lack of social contact, extreme submissiveness including withdrawal, gross motor stereotypes, a blank and expressionless face, few eye contacts, and poor *body expression*. When tested at 4 years of age, it was noted that the pattern of memory deficits was unchanged.[2] In a second set of studies,[3] the neonatal monkeys had either bilateral removal of the amygdala or the hippocampus, both with the removal of the adjacent entorhinal cortex. When tested at 10 months of age, only the animals with removal of the amygdala showed impairment of representational memory. Their deficit, however, was not as profound as that found with neonatal removal of both the hippocampus and the amygdala, suggesting that both structures contribute to the development of representational memory.

As noted by Minshew[18] and others, positron-emission tomography and nuclear magnetic resonance spectroscopy studies have indicated that there is a major disturbance in the functional organization of the cerebral cortex. This finding has also been noted in studies of event-related cortical potentials and in another evoked response, the auditory and visual negative component (NC) potentials. The former is thought to reflect nonspecific association cortices in the parietal lobe and the latter to arise from the frontal association cortex. These findings are in contrast to normal brain stem–evoked responses, also suggesting a cerebral cortical pathology. Our own observations and those of Coleman et al,[10] however, have failed to identify any consistent pathologic changes in the neocortex. We therefore speculate that the symptoms attributed to the neocortex may be reflections of the disturbed reciprocal interrelationships between the cerebral cortex and the hippocampus and amygdala. We have identified no abnormality in the thalamus in any of the brains of our study, making it unlikely that the disturbed interrelationship with the environment shown by these patients could be accounted for by an abnormality in their thalamocortical interrelationships. Also, careful search of the reticulate core of the brain stem has failed to show a recognizable change in our material.

A role of the cerebellar pathology in the symptoms of infantile autism is more difficult to understand. The classic symptoms of acquired cerebellar lesion are not a characteristic feature of infantile autism, and the effects of congenital cerebellar deficits are unknown. In terms of possible specific mechanisms, Courchesne[11] has recently suggested that the cerebellar pathology may interfere with the rapid shifting of mental focus of attention, which he notes as a deficit area in infantile autism. Our neuropathologic studies of infantile autism provide evidence for extensive involvement of the cerebellar cortex and their related nuclei in both the cerebellar hemispheres and the more medial parts of the cerebellum. Further, analysis of the pattern of morphologic changes from the younger to the older individuals provides evidence for an abnormal, persistent fetal circuit. These changes are thus in position to interfere with a broad spectrum of cerebellar functions. In this regard, Schmahmann[27] has argued for a role of the cerebellum in higher cortical function. From an extensive literature review of possible behavioral correlates of cerebellar lesions, effects of degenerative cerebellar diseases, physiologic studies, and cerebellar stimulation, he

provides evidence for a role of the cerebellum in behavior and learning. The strongest evidence that is provided for this role, however, comes from studies of the connectivity of the cerebral cortex with the cerebellum. These studies, primarily done in monkeys, have shown projections from association areas of the frontal, parietal, and temporal lobes as well as projections from the limbic cortices to the basis pontis, which in turn projects directly to the opposite cerebellar cortex via the middle cerebellar peduncle. Many of these cerebral cortical areas are associated with higher order behaviors with no direct association with motor movement or coordination. These projections from the basis pontis are mainly to the lateral lobes of the cerebellum, which in turn project primarily to the dentate and emboliform nuclei. Based on these clinical and laboratory studies, Schmahmann suggests that the cerebellar hemispheres and their associated dentate and emboliform nuclei may be involved in the modulation of thought, planning, strategy formation, spatial and temporal parameters, learning, memory, and perhaps language. The more medial parts of the cerebellum, the flocculonodular lobe, vermis, and related fastigial and globus nucleus, which are intimately related to the limbic system and hypothalamus, are postulated to be involved in primitive defense mechanisms, emotion, sexuality, and affectively important memory. There is thus evidence for widespread involvement of the cerebellum in infantile autism and clinical and experimental evidence for a role of the cerebellum in a variety of behaviors. How these two types of information interrelate is unknown and will provide a challenge for future investigators.

References

1. Arin DM, Bauman ML, Kemper TL: The distribution of Purkinje cell loss in the cerebellum in autism. Neurology 41:307, 1991
2. Bachevalier J: An animal model for childhood autism. Memory loss and socioemotional disturbances following neonatal damage to the limbic system in monkeys. Adv Neuropsychiat Psychopharm 1:129, 1991
3. Bachevalier J, Mishkin M: Effects of neonatal lesions of the amygdaloid complex or hippocampal formation on the development of visual recognition memory. Soc Neurosci Abstr 17:338, 1991
4. Bachevalier J, Mishkin M: Long-term effects of neonatal temporal cortical and limbic lesions on habit and memory formation in rhesus monkeys. Soc Neurosci Abstr 14:1, 1988
5. Bauman ML: Microscopic neuroanatomical abnormalities in autism. Pediatrics 87:791, 1991
6. Bauman ML, Kemper TL: Histoanatomic observations of the brain in early infantile autism. Neurology 35:866, 1985
7. Bauman ML, Kemper TL: Abnormal cerebellar circuitry in autism? Neurology 39:186, 1989
8. Brodal A: Modification of the Gudden method for study of cerebral localization. Arch Neurol Psychiatry 43:46, 1940
9. Brodal A: Neurological Anatomy in Relation to Clinical Medicine, ed 3. New York, Oxford University Press, 1981
10. Coleman PD, Romano J, Lapham L, Simon W: Cell counts in cerebral cortex in an autistic patient. J Autism Dev Disord 15:245, 1985
11. Courchesne E: Neuroanatomical imaging in autism. Pediatrics 87:781, 1991
12. Flechsig P: Anatomie des menchlichen Gehirn und Ruckenmarks auf myelogenetischer Grundlage. Leipzig, Georg Theime, 1920
13. Folstein SE, Piven J: Etiology of autism: Genetic influences. Pediatrics 87:767, 1991
14. Hirsh R: The hippocampus and contextural retrieval of information from memory: A theory. Behav Biol 12:421, 1974

15. Holms G, Stewart TG: On the connection of the inferior olives with the cerebellum in man. Brain 31:125, 1908
16. Mahut H, Moss M: The monkey and the sea horse. *In* Isaacson RL, Pribram KH (eds): The Hippocampus. New York, Plenum Press, 1986, pp 241–279
17. Merjanian PM, Bachevalier J, Pettigrew KD, Mishkin M: Developmental time course as well as nature of socio-emotional disturbance in rhesus monkey following neonatal limbic lesions resembling those of autism. Soc Neurosci Abstr 14:2, 1991
18. Minshew NJ: Indices of neural function in autism: Clinical and biological implications. Pediatrics 87:774, 1991
19. Mishkin M, Appenzeller T: The anatomy of memory. Scientific American 256:80, 1987
20. Murray EA: Representational memory in nonhuman primates. *In* Kesner RP, Olton DS (eds): Neurobiology of Comparative Cognition. Hillsdale, NJ, Lawrence Erlbaum Associates, 1990, p 127
21. Nelson KB: Prenatal and perinatal factors in the etiology of autism. Pediatrics 87:761, 1991
22. Overmann WH: Performance on traditional match-to-sample, nonmatch-to-sample, and object discrimination tasks by 12 and 32 month-old children: A developmental progression. *In* Diamond A (ed): Development and Neural Bases of Higher Cognitive Function. New York, Academic Press, 1990, pp 365–393
23. Rakic P, Sidman RL: Histogenesis of cortical layers in human cerebellum particularly the lamina dissecans. J Comp Neurol 139:473, 1970
24. Rapin I: Autistic children: Diagnosis and clinical features. Pediatrics 87:751, 1991
25. Raymond J, Bauman M, Kemper TL: The hippocampus in autism: Golgi analysis. Ann Neurol 26:483, 1989
26. Ritvo ER, Freeman BJ, Scheibel AB, et al: Lower Purkinje cell counts in the cerebellum of four autistic subjects: Initial findings of the UCLA-NSAC autopsy research reports. Am J Psychiatry 143:862, 1986
27. Schmahmann JD: An emerging concept. The cerebellar contribution to higher function. Arch Neurol 48:1178, 1991
28. Scoville WB, Milner B: Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 20:11, 1957
29. Squire LR, Zola-Morgan S: The medial temporal lobe memory system. Science 253:1380, 1991
30. Stanfield BB, Cowen WM: The development of the hippocampus. *In* Peters A, Jones EG (eds): Cerebral Cortex, vol 7. New York, Plenum Press, 1988, p 91

Address reprint requests to

Thomas L. Kemper, MD
Department of Neurology
Medical 9
Boston City Hospital
818 Harrison Avenue
Boston, MA 02118