The Development of the Pathologic Changes of Alzheimer's Disease and Senile Dementia in Patients with Down's Syndrome

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Senile plaques, neurofibrillary change and granulovacuolar degeneration characterize Alzheimer's disease (presenile dementia) and senile dementia and are also seen in the aged human brain. The development of these lesions was studied in 13 patients with Down's syndrome, ages 12 to 65, with the purpose of defining similarities and dissimilarities, if any, between their morphologies in these four conditions. Evaluation by light and, when applied, electron microscopy established apparent identities. The findings suggest that Down's syndrome, with its partially characterized genotypic and phenotypic abnormalities, is an appropriate model for the study of the pathogenesis of these lesions (Am J Pathol 73:457–476, 1973).

ALZHEIMER'S DISEASE (presenile dementia) and senile dementia are similarly characterized morphologically by senile plaques, Alzheimer's neurofibrillary change and granulovacuolar degeneration and are therefore increasingly recognized as identical diseases, being distinguished only by the age of onset of the dementia.[1] The same morphologic lesions also occur, but generally with lesser severity, in certain other human pathologic states,[2,3] and in the brains of aged persons without overt dementia.[4]

The prevalence and socioeconomic significance of these two dementias have prompted searches for experimental models suited to defining the etiology and pathogenic mechanisms in these diseases. Senile plaques have been observed in some aged animals,[5,6] while neurofibrillary alterations and plaque-like lesions have been produced experimentally in other animals.[6] However, the natural and induced animal lesions differ structurally from their counterparts in humans.[3,5,6]

It has become increasingly apparent that the patient with Down's syndrome is especially likely to develop the pathologic and often some of the clinical features of Alzheimer's disease or senile dementia.[1] We have studied the autopsy findings of a series of patients with Down's syndrome, with a view towards evaluating this natural pre-

dilection as a source of information about the pathogenesis and eti-
ology of Alzheimer's disease and senile dementia. It was first nec-
cessary to establish the similarities and dissimilarities between the
morphologic expressions of these disorders in patients with and with-
out Down's syndrome. The findings are in general accord with previ-
ous reports; [1,7–13] they disclose that the development of senile plaques
neurofibrillary tangles and granulovacuolar change are predictable
events by early middle age. The present studies extend these obser-
vations to the ultrastructural level and establish more precisely the
similarities between the morphologic lesions of Alzheimer's disease
and senile dementia and those that occur regularly and precociously
in Down's syndrome. Although the findings do not offer an under-
standing of the pathogenesis of these disorders, they suggest that the
etiologic factors be sought in the genotypic and/or phenotypic setting
of Down's syndrome.

Materials and Methods

The brains of 13 patients (Table 1) with Down's syndrome were examined in
detail by light microscopy, and representative tissues of 3 were studied also by
electron microscopy. The clinical diagnosis of this syndrome had been estab-
lished in each case by the phenotypic appearance and by mental retardation.
Chromosomal studies were not available. The ages of the patients at the time of
death ranged from 12 to 65 years.

The brains were examined grossly for the presence of congenital abnormalities,
cerebral cortical atrophy and atherosclerosis. In each case, histologic sections were
prepared of the frontal lobes and hippocampus; in most cases, representative
sections were made from other areas of the brain. The tissues were embedded in
paraffin and sections were stained by hematoxylin and eosin, hematoxylin and
eosin–Luxol fast blue, periodic acid–Schiff, Perls', alizarin red, oil red O, Congo
red, alcian blue, Holmes, or a silver impregnation stain as described by King.[14]
With the exception of cases 1, 3 and 4, the King silver stain was also performed
on frozen sections of nonembedded formalin-fixed tissues. The light microscopic
evaluations were made with special attention to the quantitative and qualita-
tive properties of three changes: senile plaque formation, neurofibrillary change
and granulovacuolar degeneration.

For electron microscopy, formalin-fixed tissues were postfixed in osmium
tetroxide, dehydrated through graded ethanols and embedded in Epon. Tissues
examined by electron microscopy included the hippocampus and frontal lobes of
cases 5 and 8, and the hippocampus in case 13.

Results

Gross Observation

In their gross configurations, most of the brains showed features
characteristic of Down's syndrome: a flattening of the frontal and
occipital poles, a perpendicular insertion of the brain stem into the

Table 1—Summary of Autopsy Findings in Brains of Patients with Down's Syndrome

Case No.	Age (yrs), race, sex	Brain wt (g)	Cortical atrophy	Senile plaques		Neurofibrillary change		Granulovacuolar degeneration
				Frontal lobe	Hippocampus	Frontal lobe	Hippocampus	Hippocampus
1	12 W F	1200	0	0	0	0	0	0
2	17 W M	700*	0	2+	1+	0	0	0
3	18 W M	1080	0	0	0	0	0	0
4	19 W M	1250	0	2+	1+	0	0	0
5	31 W F	1230	0	2+	3+	0	0	0
6	38 B F	1030	0	3+	3+	0	2+	1+
7	52 W F	940	3+	3+	3+	1+	3+	2+
8	53 W M	930	3+	3+	3+	2+	4+	3+
9	55 W F	880	3+	3+	3+	1+	3+	3+
10	57 W F	980	3+	3+	3+	2+	3+	2+
11	59 W M	1200	0	3+	3+	1+	3+	2+
12	62 W M	1050	0	4+	4+	2+	3+	3+
13	65 W M	765	4+	3+	3+	2+	4+	3+

* Extensive ulegyria was present in this case

cerebrum,[15] and in several cases a relatively small cerebellum (Figures 1–4.[16] No other congenital abnormalities, such as a tuber flocculum were seen. In case 8 (Figures 3 and 4), the superior temporal gyrus was small, but this appeared to be the result of atrophy rather than a congenital underdevelopment. The brain weights as expected [17] were generally less than normal (Table 1), ranging from 700 (case 2) to 1250 g (case 4). In the younger patients (cases 1–6), although the brains were usually small, the gyri were full, the sulci narrow and the ventricles of normal size (Figures 1, 2). The brains of 5 of the 7 older patients (cases 7–10 and 13) showed significant cortical atrophy compensated by dilated lateral ventricles (Figures 3 and 4; Table 1). Atherosclerosis was notably minimal in the major vessels at the base of the brain, as well as in the intraparenchymal vessels. This was a conspicuous negative finding in the older age group when compared to control specimens from patients of comparable ages without Down's syndrome.

Microscopic Observations

Senile Plaques

Senile plaques were most readily visualized in tissue stained by the King method, appearing as focal spherical aggregates or argyrophilic material. They were identified in all cases except 1 and 3 (Table 1). In these two cases, tissues were not available for frozen section and the King stain was applied to paraffin-embedded sections, a technic that diminished the quality of the stains and lessened the opportunity to identify plaques. Because of this limitation, there remains some uncertainty about the age of onset of plaque formation in the present series. However, the brain of a 5-year-old patient with Down's syndrome did not show demonstrable plaques when extensively studied with optimum technics. The plaques in the younger individuals (cases 2, 4–6) were formed of delicate webs of argyrophilic neurites that blended somewhat indistinctly into the surrounding neural tissues. They did not contain neurons with neurofibrillary change, nor was there stainable amyloid, sudanophilic lipid or PAS-positive material (Figure 5). In the older individuals, the plaques were more discrete; they occasionally contained neurons showing neurofibrillary change and microglial cells, and usually demonstrated a central dense core containing stainable amyloid, sudanophilic lipid and PAS-positive substance (Figure 6). The plaques of the younger individual could not be identified with the hematoxylin and eosin–

Luxol fast blue or the alcian blue stain, although they could be in the older age group. Consistently, plaques were most numerous in the frontal lobes and hippocampus and were of approximately the same density in these two areas. These plaques, in cases 5, 8 and 13, were seen by electron microscopy to consist of dilated neurites filled with abnormal mitochondria, dense bodies and lipid (Figure 7), indistinguishable from those seen in Alzheimer's disease and senile dementia.[1,6] In case 5 extracellular fibrillar material, structurally consistent with amyloid, was present centrally in the plaques (Figures 7), although this material was not seen in tissue from this case stained by Congo red and examined by light microscopy.

Neurofibrillary Change

Neurofibrillary change was also identified by the King stain and consisted of argyrophilic bundles coursing in the perikaryon and the proximal processes of the neurons (Figures 6 and 8). This change was evident in cases 6–13 (Table 1). In case 6, it was a feature of a small number of neurons solely in the hippocampus, while in the older cases it was found both there and in the frontal cortex. In all cases, considerably more neurofibrillary change was present in the hippocampus, especially the glomerular formation (Figure 8), than in the frontal lobe (Figure 6). The degree of neurofibrillary change generally appeared to correlate with the amount of cerebral cortical atrophy. When viewed by electron microscopy (cases 8 and 13) this argyrophilic material appeared as sheaths of "twisted tubules" (Figures 9–11) identical in their fine structure to those which characterize Alzheimer's disease.[3,18] In the present material, these tubules had a maximum and minimum width of 200 and 100 Å, respectively, and showed a periodic constriction approximately every 800 Å (Figure 10). On cross-section, these profiles were round or comma-shaped (Figure 11).

Granulovacuolar Degeneration

Granulovacuolar degeneration appeared in the perikaryon of neurons as clear vacuoles containing small dense granules (Figure 12). Pyramidal neurons in Ammon's horn of the hippocampus were selectively involved, although in case 7, a few neurons of the insular cortex also showed this same alteration. Granulovacuolar degeneration was present in cases 6–13 (Table 1). In case 6, only a small number of neurons showed this specific form of degeneration. Beyond this age the change was more extensive.

Other Microscopic Features

In the hippocampal cortex of case 8, within what appeared to be neuronal processes, were structures which were visible only by electron microscopy (Figure 13). These were formed of parallel lattices, made up of approximately 100-Å filaments. The globus pallidi were available for study in 10 patients. In cases 1, 2, 5–7 and 13 there was mineralization of the blood vessels that stained positively for iron and calcium.

Discussion

This study is in accord with others [1,7–13] and makes it clear that the patients with Down's syndrome predictably and precociously develop fully and precisely the morphologic expression of Alzheimer's disease and senile dementia at or before the fourth decade.

It is apparent from our series that the formation of senile plaques considerably antedates neurofibrillary change and granulovacuolar degeneration. Plaques were present in small numbers in the second decade and increased numerically in the third. Initially the plaques were loosely structured and did not contain a central core of amyloid, sudanophilic lipid or PAS-positive material, nor did they contain neurons showing neurofibrillary alterations. Plaques observed in the fourth and subsequent decades, however, were more discrete and their cores contained the above material and occasionally neurons with neurofibrillary change. While there are inherent limitations in the reconstruction of sequential events from static morphologic lesions, nevertheless, the present observations strongly suggest that the senile plaque undergoes sequential structural changes. It has been suggested that the forerunner or earliest change in the development of the senile plaques is recognized by electron microscopy as dilatation of neurites in a focal area, wherein there is engorgement by mitochondria and dense bodies.[6,19] In agreement with the present observation, these investigators noted that the extracellular amyloid was deposited at a later time. By the nature of the postmortem material, the present studies were largely restricted to light microscopy; thus amyloid may have been present in small amounts at an earlier time than was recognized by this technic. This possibility was underscored by case 5.

The plaques in the patient with Down's syndrome, as well as those in patients with Alzheimer's disease and senile dementia, should be contrasted with those that occur naturally or experimentally in animals. The natural lesions in aged dogs contain amyloid, but "twisted

tubules," a distinctive feature of the human lesions, have not been observed.[5] The experimentally produced plaques contain neither amyloid nor twisted tubules.[6]

Neurofibrillary change, as observed in the present series, clearly occurred later than did the senile plaque and preferentially involved the hippocampus. In patients of older age, neurofibrillary tangles were present also in neurons of the cortex, but were always more prominent in the hippocampus. A similar temporal relationship between the formation of senile plaques and neurofibrillary change was noted in patients with Down's syndrome by Haberland.[7] In her study of 6 patients, ages 34–74 years, senile plaques were consistenly present, but neurofibrillary change was noted only in the older (ages 52, 56, 74).

It has been demonstrated that the bundles of argyrophilic material which constitute the neurofibrillary changes in Alzheimer's disease and senile dementia consist of aggregates of twisted tubules.[3] The neurofibrillary tangles seen by electron microscopy in the present material (cases 8 and 13) were likewise formed of twisted tubules with identical morphology. Neurofibrillary alterations can be produced experimentally in animals but these lesions are characterized ultrastructurally by aggregates of 100-Å filaments rather than twisted tubules.[3,20] Thus, like the senile plaque, neurofibrillary change in Down's syndrome is structurally indistinguishable from that which occurs in Alzheimer's disease and senile dementia, and is in contrast to lesions in animals.

Granulovacuolar degeneration paralleled neurofibrillary change in severity and was also seen only in the older patients. It appeared by light microscopy to be identical to that in Alzheimer's disease and senile dementia. Because of the degree of postmortem change in the present material, this lesion was not studied at the ultrastructural level.

The lattice-like structures in case 9 appear similar to the Hirano body.[21–23] This inclusion, first described in the Guam-Parkinson-dementia-complex,[21] has also been seen in Alzheimer's disease and in a number of other conditions.[23] Its presence in Down's syndrome provides a further, though not great, structural analogy between the brain in aging patients with Down's syndrome and the brain in patients with Alzheimer's disease and senile dementia.

Since the pathologic features of Alzheimer's disease and senile demential are paralleled precisely in Down's syndrome, the question arises whether in the latter, as in the former, there is a concomitant appearance of dementia. In the studies of a series of brains from patients

with no evidence of Down's syndrome with and without dementia, Tomlinson *et al* concluded that large numbers of senile plaques, conspicuous granulovacuolar degeneration and extensive neurofibrillary change, especially in the cortex, is almost inevitably associated with dementia,[24] while these morphologic changes can be present in lesser degrees without overt dementia.[4] Considering the large numbers of senile plaques and extensive granulovacuolar degeneration and neurofibrillary change in patients with Down's syndrome by the fourth decade, one might reasonably expect that the state of mental retardation in these patients would be compounded by dementia. Although mental deterioration has been frequently noted in elderly patients with Down's syndrome, such findings have not been uniformly documented, even though extensive Alzheimer's changes were evident on postmortem examination. In a discussion of elderly patients with Down's syndrome, Jervis,[9] for example, noted the absence of distinguishable personality change. Olson and Shaw,[13] however, recorded deterioration in the mental function of a 57-year-old patient with Down's syndrome whose brain demonstrated the typical features of Alzheimer's disease or senile dementia. These authors reviewed and tabulated the findings of 41 cases of Down's syndrome from the literature, added 4 of their own, and indicated that in over 8 of the total cases, dementia was present. Haberland [7] reported personality changes that began in 2 patients with Down's syndrome at ages 36 and 24. When death occurred at ages 56 and 39, respectively, marked changes of Alzheimer's disease were present in the former but only mild changes were present in the latter. In a clinical study, Owens *et al* [25] examined living patients with Down's syndrome for signs of mental deterioration. In a comparative study of a group of patients age 35 to 50, with a younger group age 20 to 25, these authors were unable to identify clinical evidence of "Alzheimer's disease," even in the former, but suggested that these older patients demonstrated a "higher incidence of frontal lobe and diffuse cerebral dysfunction." Thus, while there is evidence that the older patients with Down's syndrome do show mental changes, the precise functional correlation between the morphologic expression of Alzheimer's disease and Down's syndrome and the appearance of dementia requires further documentation.

The structural identity of the changes in Down's syndrome to those of Alzheimer's disease and senile dementia, their inevitable appearance before the fourth decade, coupled with the dissimilarities between these changes and those that occur naturally or experimentally in

animals, underscore the value of this natural syndrome with its already partially characterized metabolic abnormalities as a potential source of information relative to the genesis of these naturally occurring human lesions. The described metabolic abnormalities in Down's syndrome are numerous; for simplicity, they can be grouped as a) immunologic and b) biochemical.

The immunologic abnormalities have received much attention because of the propensity of patients with Down's syndrome for infection. Plasma IgG,[26,28] IgA[29] and IgD[27] levels are elevated, while the IgM levels have been reported both as reduced [28] or slightly elevated.[29] The elevated levels of IgG, IgA and IgD may be the result of frequent infections rather than an indication of a primary immunologic disorder. Cultured lymphocytes from patients with Down's syndrome show a decreased response to phytohemagglutinin as evidenced by a decreased DNA polymerase activity, tritiated thymidine uptake and RNA response.[26] "Partial leukocyte dysfunction" to staphylococci [30] has been reported, as well as a shortened leukocyte life-span.[26] Although the three lesions described above in the brain of aging patients with Down's syndrome do not generally suggest a response to an immunologic injury, the presence of amyloid in the senile plaque might be an expression of an immunologic dysfunction.

Many biochemical abnormalities have been described in Down's syndrome. The best documented are leukocytic and erythrocytic enzymatic alterations and changes in various aspects of amine metabolism. Increased activities of leukocytic galactose-l-phosphate uridyl transferase, alkaline phosphatase, acid phosphatase and glucose-6-phosphatase have been reported, as have increased activities of erythrocytic phosphohexokinase and serum glutamic oxaloacetic transaminase.[26] It is, at this time, difficult to relate these abnormalities to the morphologic lesions under discussion.

The best documented abnormality of amine metabolism in young patients with Down's syndrome consists of a decreased whole blood and platelet level of serotonin, both probably due to low platelet uptake and binding of this compound.[31,32] In the cerebrospinal fluid, however, levels of two serotonin metabolites, 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) have been reported as normal.[32] In the blood, a decreased plasma level of dopamine-β-hydroxylase has been reported in children with Down's syndromes although the levels became normal in adults.[33] A possible chemical link between Down's syndrome and presenile and senile dementia is indicated in reports demonstrating decreased cerebrospinal fluid levels of 5-HIAA and HVA

in patients with presenile and senile dementia.[34-36] The specificity of these abnormalities can be questioned, however, as a reduced cerebrospinal fluid level of HVA has also been shown in Parkinsonism[35] and in depression.[37] Thus, while amine abnormalities occur in both patients with Down's syndrome and in those with Alzheimer's disease and senile dementia, they are not identical and may be coincidental or secondary expressions of the diseases.

The metabolic derangements in Down's syndrome presumably reflect the abnormal genotype. These derangements have been suggestively evidenced at the cellular level in the subnormal capacity of fibroblasts for replication in vitro.[38] Although there is no knowledge that defines the pathogenic relationship between this abnormal metabolic state and senile plaque formation, neurofibrillary change and granulovacuolar degeneration, or to what degree "environmental" factors contribute in their causation, the morphologic identity between these lesions in Down's syndrome, Alzheimer's disease, senile dementia and the aged human brain clearly defines Down's syndrome as an appropriate and potentially fruitful source of such information.

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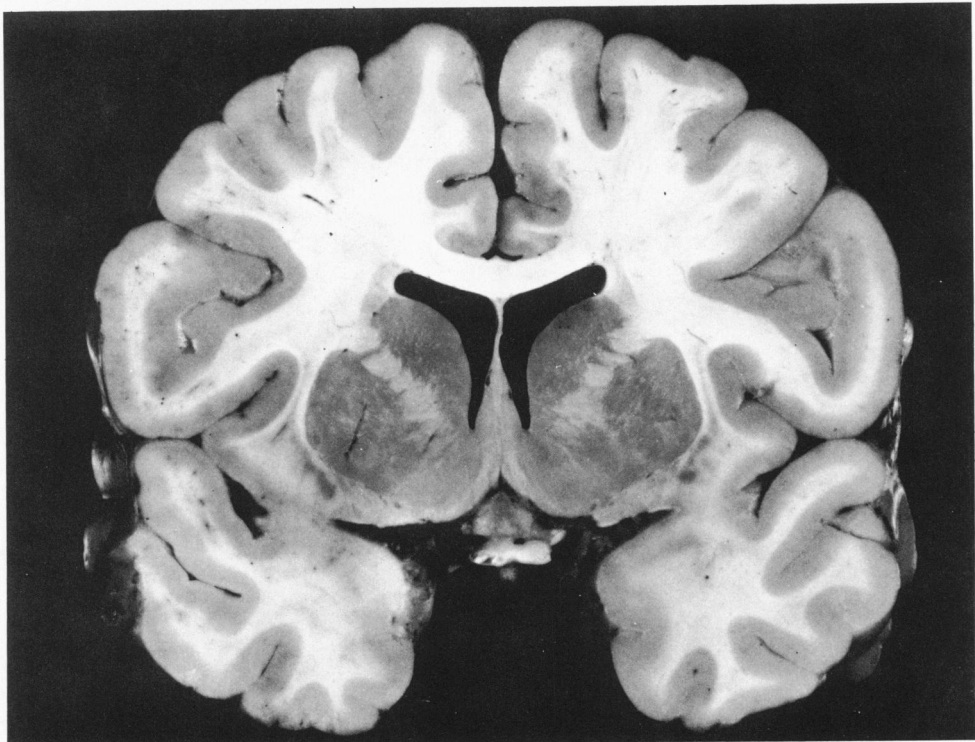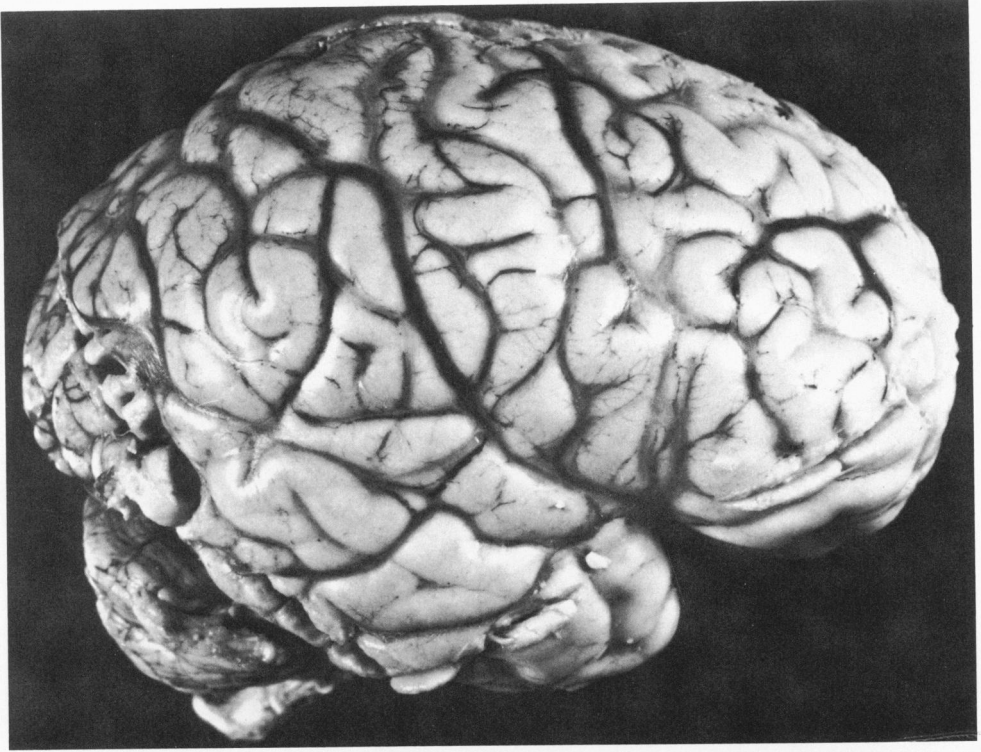
Figs 1 and 2—Lateral and coronal views of the brain of case 5 (31 years). The gyri are full, the sulci narrow and the lateral ventricles of normal size. There is slight flattening of the frontal and occipital poles.
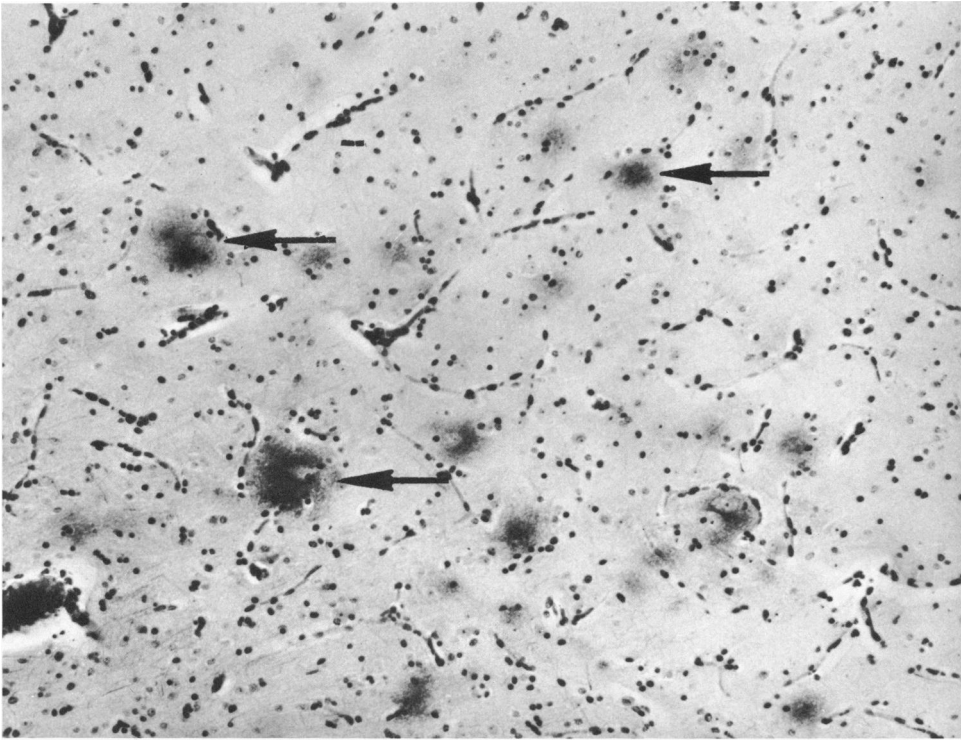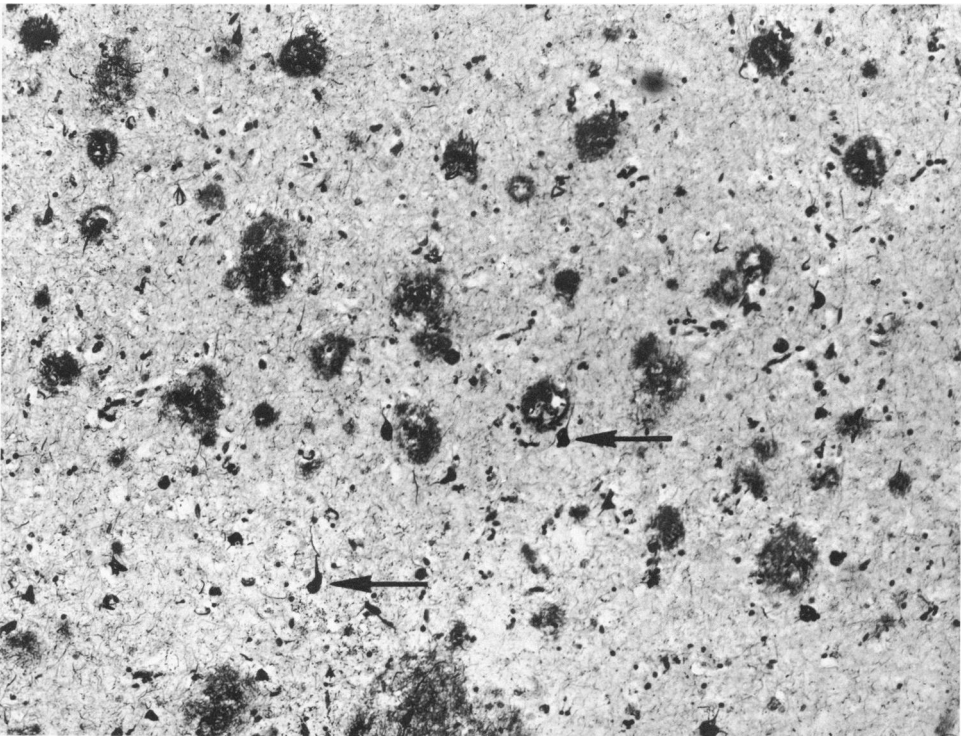
Figs 3 and 4—Lateral and coronal views of the brain of case 8 (53 years). There is marked cortical atrophy as evidenced by narrow gyri, wide sulci and dilated lateral ventricles. The atrophy is more prominent in the frontal and temporal lobes. The fontal and occipital poles are somewhat blunted.

Fig 5—Scattered senile plaques (*arrows*) in the frontal lobe of case 2 (17 years) consist of loose aggregates of argyrophilic neurites (King silver stain, × 120).   **Fig 6**—Many dense senile plaques, as well as neurons showing neurofibrillary change (*arrows*) are present in the frontal lobe of case 8 (53 years) (King silver stain, × 120).

Fig 7—Electron micrograph of a senile plaque in the hippocampus of case 5. The plaque is formed of neurites (*hatched lines*) filled with dense bodies. Amyloid fibrils are present (*arrows*). A=myelinated axon ($\times$ 7000).

Fig 8—The glomerular formation of the hippocampus of case 13 shows many neurons filled with argyrophilic material (neurofibrillary change). A moderate number of senile plaques are present (King silver stain, $\times$ 120).
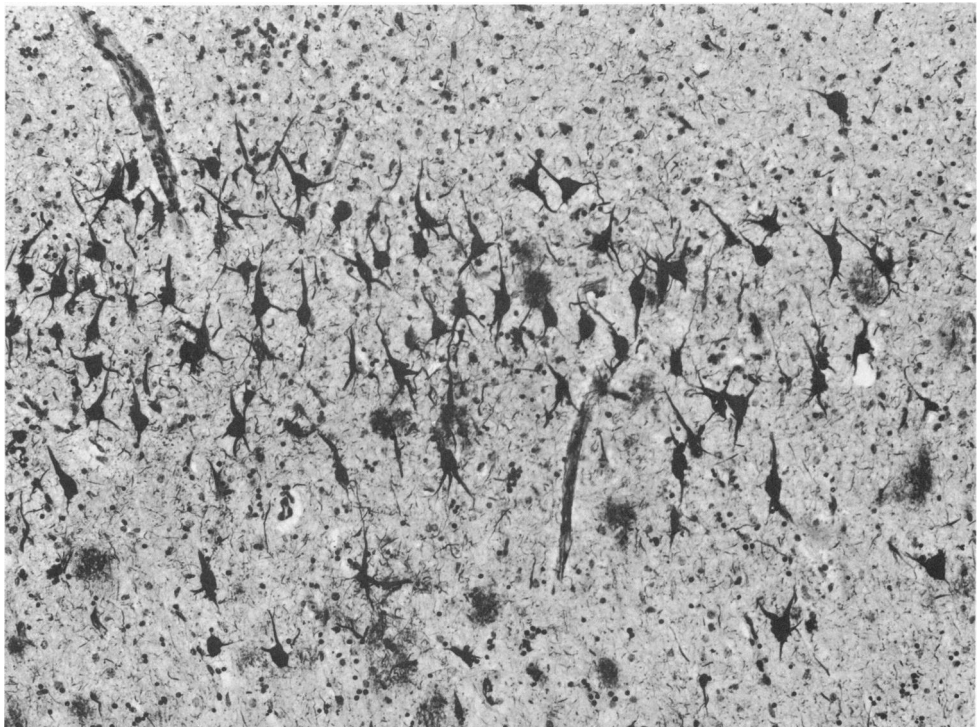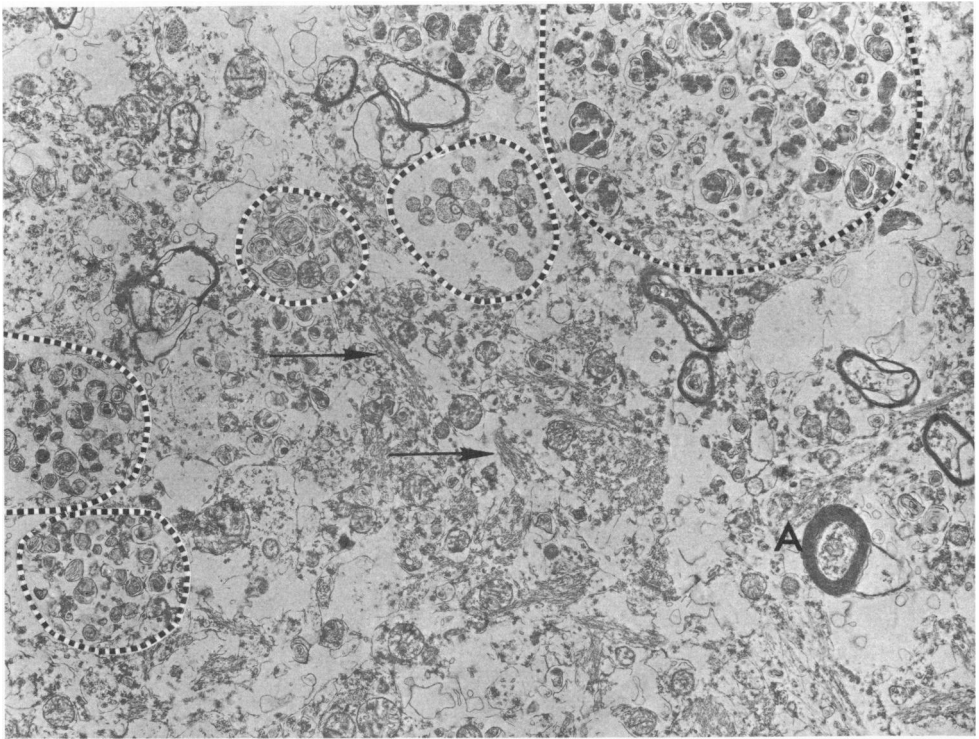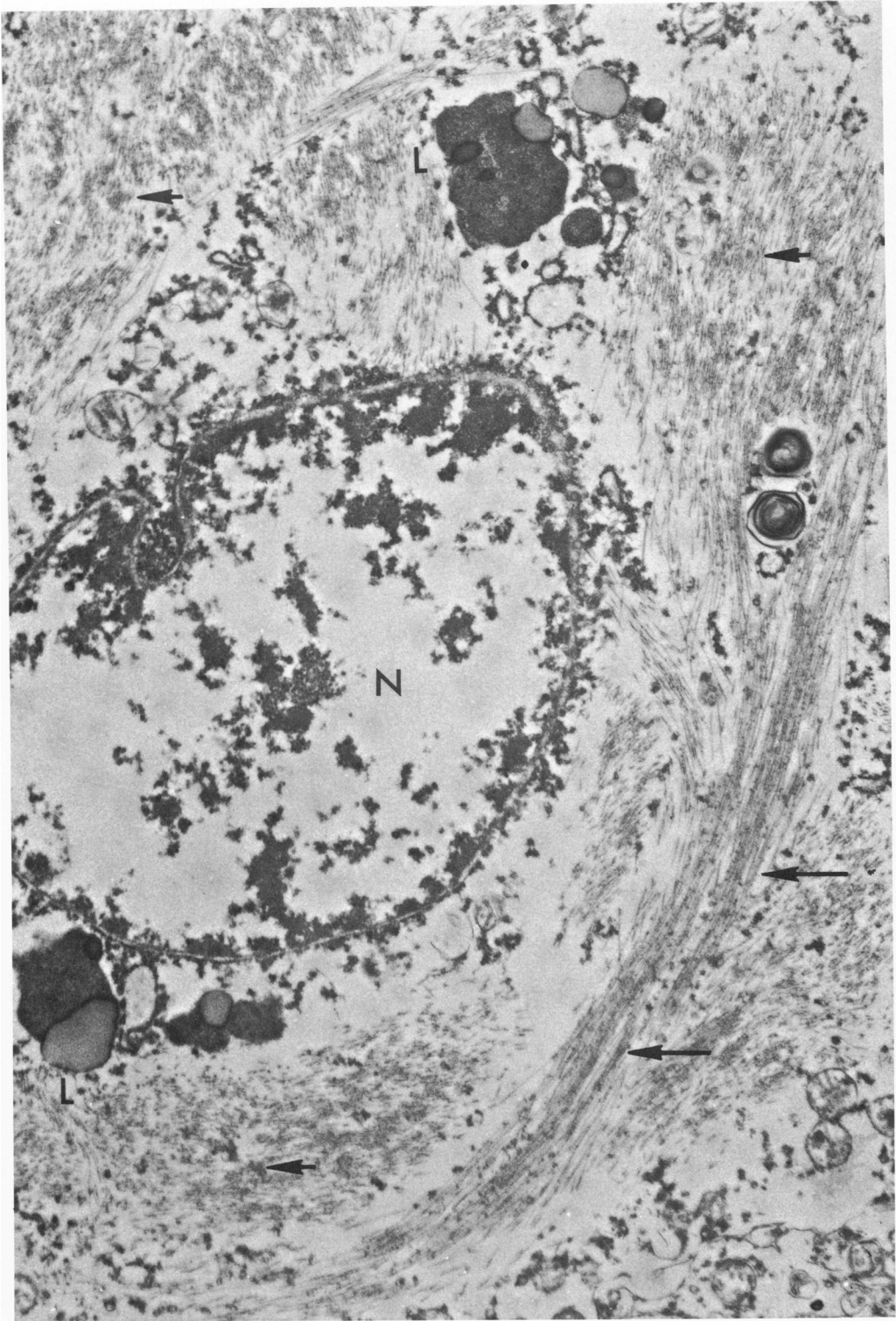
Fig 9—Electron micrograph of a neuron from the hippocampus of case 13 shows neurofibrillary change. At this magnification, the argyrophilic material that is shown by light microscopy in the neuronal perikaryon and proximal processes in Figures 6 and 8 appears as sheaves of filamentous material. It is shown in longitudinal section (*large arrows*) and in cross or oblique section (*short arrows*). *N*=nucleus, *L*=lipofuchsin (× 14,000).
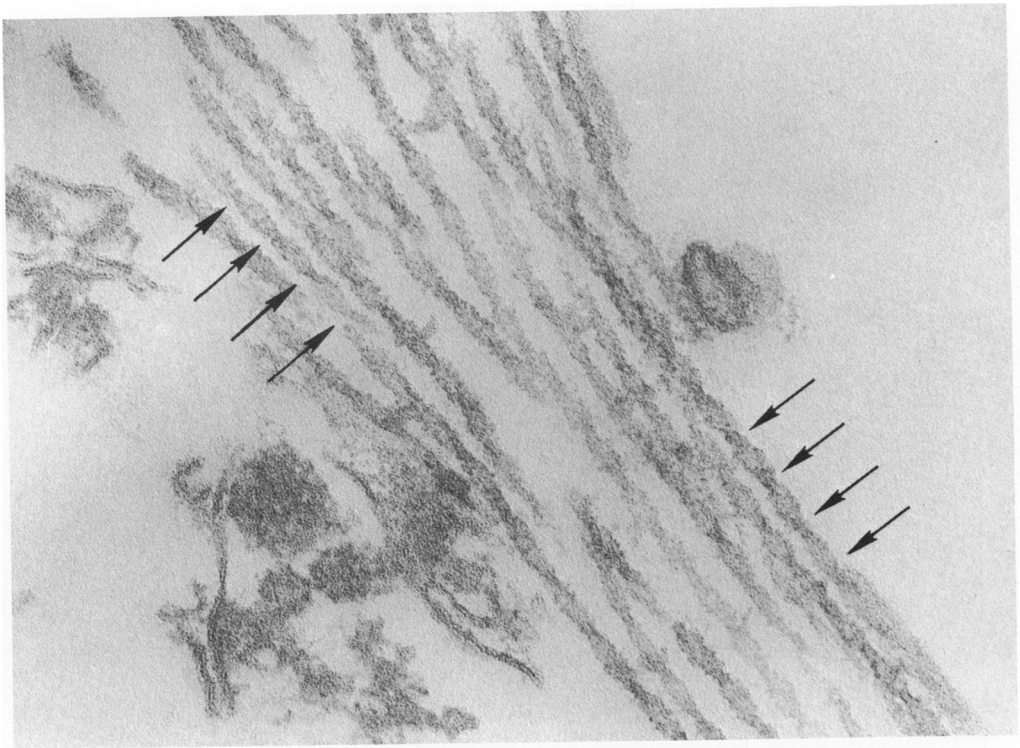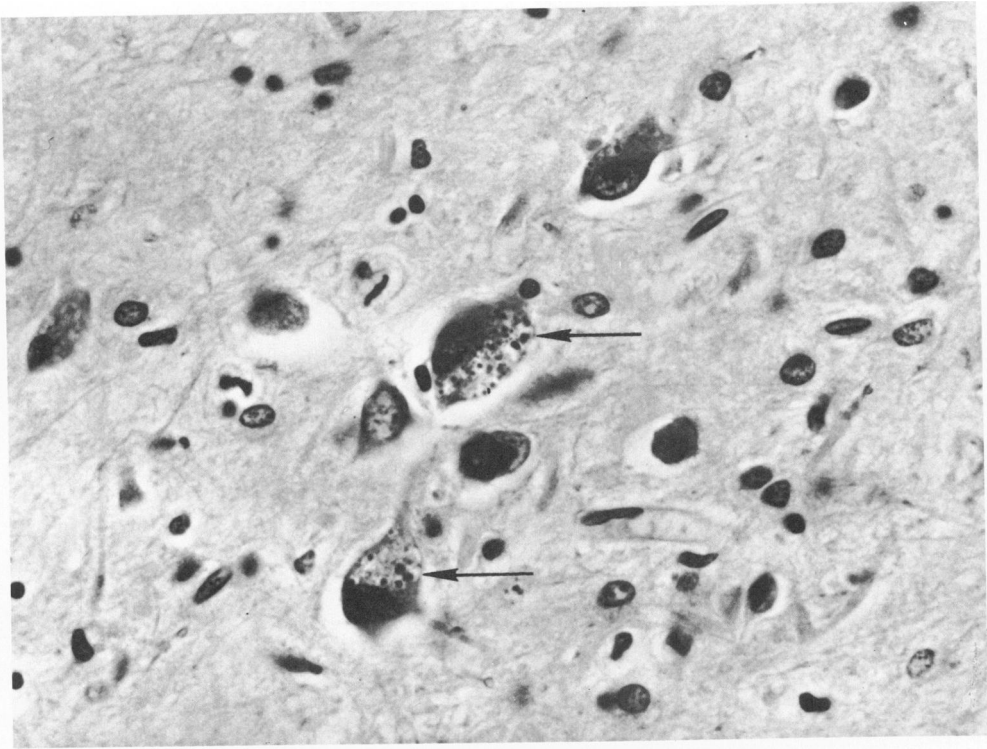
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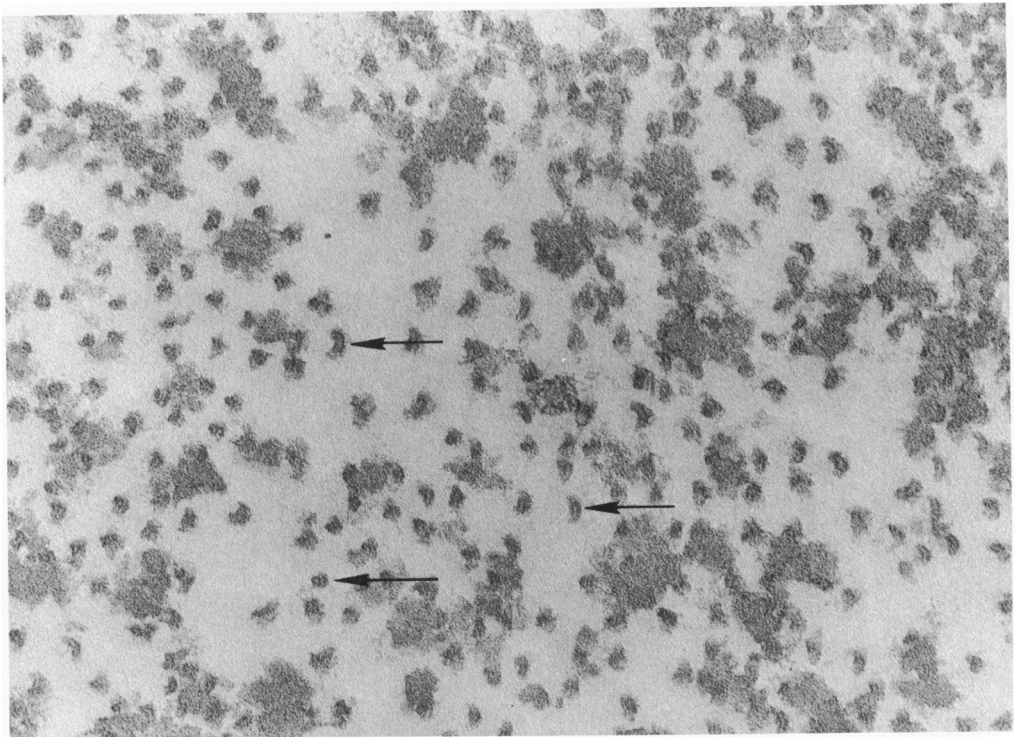
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Fig 10—Higher magnification of the filamentous material (twisted tubules) is shown in longitudinal section. Note the constrictions (*arrows*) with periodicity of approximately 800 Å. Case 13 (× 117,000).   **Fig 11**—In cross section, the twisted tubules shown in Figure 10 are circular or comma-shaped (*arrows*). Case 13 (× 117,000).
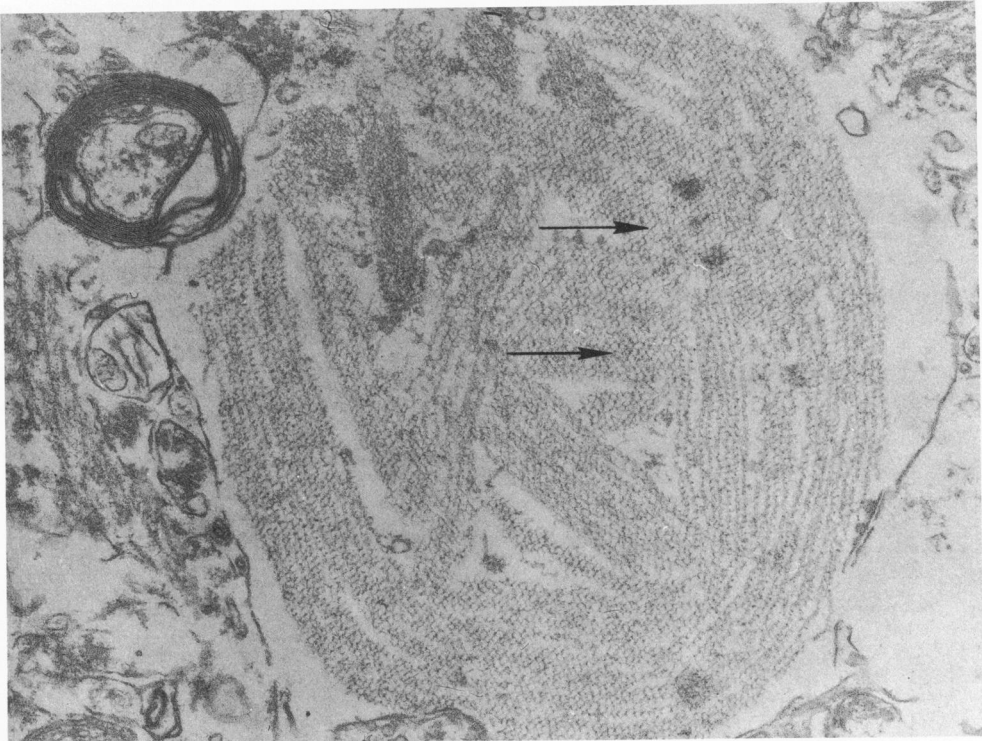
Fig 12—Granulovacuolar degeneration in the hippocampal neurons of case 12. The cytoplasmic vacuoles contain a basophilic granule (*arrows*) (Hematoxlin and eosin/Luxol fast blue, × 480).　　Fig 13—A Hirano body in the hippocampus of case 5. The lattice-like nature of this structure is best appreciated at *arrows* (× 40,000).