Neurofibrillary Tangles in the Dementia of "Normal Pressure" Hydrocephalus

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SUMMARY: *Routine neuropathological examination could not explain the dramatic improvement exhibited by one patient with "normal pressure" hydrocephalus after shunting. The improved patient contrasted remarkably with the unchanged condition of four others also shunted successfully. The five brains were analysed by quantitative morphometry to determine the degree of neurofibrillary tangle formation in mesial temporal neurons. The density of tangle-bearing nerve cells in the four unimproved cases was markedly greater than in age-matched control brains from nineteen normal subjects, and fell in the same range as that of eight dements with neuropathologically confirmed Alzheimer's disease. The density of the one who recovered was within normal limits.*

The duration of dementia before shunting, and the total duration of dementia in these five patients rank in the same order as their degree of neurofibrillary formation. Furthermore, a positive linear correlation exists between the Tangle Indices and the total duration of dementia. The data suggest that early diagnosis may improve the chances of reversing the dementia of normal pressure hydrocephalus before histological alterations prove too severe.

RÉSUMÉ: *Un examen neuropathologique de routine ne pourrait expliquer l'amélioration marquée après "shunting" exhibée par un patient avec hydrocéphalie normotensive, quand on la compare avec celle de quatre autres patients également opérés avec succès dont la condition est demeurée inchangée. Les cinq cerveaux furent analysés par morphométrie quantitative pour déterminer le degré de développement des formations neurofibrillaires dans les neurones mésio-temporaux. La densité des cellules nerveuses porteuses de formations neurofibrillaires dans les quatre cas non améliorés était remarquablement plus grande que dans les cerveaux contrôles de dix-neuf sujets normaux du même âge, et était du même ordre de grandeur que celle de 8 déments atteints de maladie d'alzheimer confirmée neuropathologiquement. La densité de ces cellules anormales chez celui qui fut guéri était dans les limites de la normale.*

La durée de la démence avant l'opération et la durée totale de la démence chez ces cinq patients s'échelonnaient selon le même ordre que leur degré de formation neurofibrillaire. En plus, une corrélation positive linéaire existe entre l'indice des formations neurofibrillaires et la durée totale de la démence. Ces données suggèrent qu'un diagnostic précoce pourrait augmenter les chances de réversion de la démence dans l'hydrocéphalie normotensive avant que les altérations histologiques ne soient trop sévères.

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INTRODUCTION

Since the report of Adams et al (1965) of dramatic cures from shunting of hydrocephalic patients with dementia, ataxic gait, and incontinence, the syndrome of "low pressure" or "normal pressure" hydrocephalus (NPH) has intrigued clinical neuroscientists. Several unsolved mysteries of this disease remain (Sugar, 1976). The biophysical mechanism of its development, which should link the altered cerebrospinal fluid (CSF) dynamics with the symptoms and signs, is not clear (Hakim and Adams, 1965; Geschwind, 1968; Ojemann et al, 1969). The clinical and laboratory criteria required to substantiate the diagnosis are imprecise (Messert and Wannamaker, 1974). Despite numerous radiographic studies (pneumoencephalography, radioisotope scans, angiography, echoencephalography, computerized axial tomography) and other laboratory investigations (e.g., electroencephalography; saline intrathecal infusion manometry), no single examination or combination of clinical and laboratory abnormalities has been found that will predict which patients with the syndrome will respond favorably to shunting procedures (Bannister, 1972; Wolinsky et al, 1973; Adapon et al, 1974; Stein and Langfitt, 1974).

To date, very few patients with NPH, whether shunted or not, have been studied at autopsy. The brains of two patients treated unsuccessfully by ventriculoatrial shunt (Lorenzo et al, 1974) were said to have multiple lacunes, consistent with their histories of systemic hypertension; and one of these also showed arteriolar sclerosis and foci of demyelination in the centrum

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semiovale, characteristic of Binswanger's subcortical hypertensive encephalopathy.

Ernest et al (1974) reported necropsy findings on two patients who had had diabetes and systemic hypertension, both of whom were considered to have clinical and radiographic changes typical of NPH. Their 66 year-old man had a moderately good response to ventriculoperitoneal shunt and expired of hypertensive cardiac disease one year later. Their 45 year-old woman died unimproved only a month after ventriculojugular shunt, of pulmonary embolism. Both brains contained many old cystic "lacunar" infarcts throughout cerebrum and cerebellum, but especially in the basal ganglia. The authors suggested that the initial pathological process in some cases of NPH might be hypertensive cerebrovascular disease with the "lacunar state" (multiple small infarcts) in deep cerebral grey matter.

The brains of four other "idiopathic" cases of NPH have shown fibrous and obliterative thickening of the leptomeninges, at the incisura tentorii or over the cerebral convexities (Heinz et al, 1970; DeLand et al, 1972; Sypert et al, 1973). The cause of the subarachnoid obstruction was unclear in three, and secondary to old subarachnoid hemorrhage in the fourth. Two further patients with CSF dynamics indicative of NPH showed Alzheimer's disease at post-mortem examination (Sohn et al, 1973; Coblentz et al, 1973).

In this report we document the autopsy findings on five people shunted for NPH, four of whom showed no response and one of whom improved dramatically. With quantitation of the neurofibrillary tangle formation in the mesial temporal cortex of these brains, a striking difference was found which may explain the lack of recovery in the four unchanged patients.

Clinical and Pathological Data

The first patient, a 78 year-old retired personnel manager (Patient No. 21 in the series to be discussed), was admitted to hospital at age 76 with an ataxic gait. His wife also noted increasing loss of memory for the previous five months and loss of interest in daily affairs. There was no urinary incontinence. Blood pressure on examination was 240/120 mm. Hg. In addition to inappropriate moods including crying without provocation and poor concentration, the man exhibited a positive glabellar tap, a sometimes shuffling gait, and a tremor of the hands, suggesting some Parkinsonian element to his problem. CSF pressure at lumbar puncture was 110 mm. The cerebrospinal fluid was normal. Pneumoencephalography showed marked dilatation of the lateral ventricles and the third venticle, with some air in widened cortical sulci over the Sylvian regions although none over the frontoparietal convexities. Radioiodine-labelled human serum albumin (RHISA) scan of CSF by lumbar injection showed most of the CSF flow was abnormal, entering the ventricles in a retrograde direction. A little radioisotope did, however, migrate slowly over the lateral aspects of the hemispheres, although almost none reached the vertex. Pertechnitate brain scan and EEG were not contributory.

While in hospital, he developed a mild spastic quadriparesis, with hypertonic, hyperreflexic limbs. The patient was discharged with the diagnosis of "normal pressure" communicating hydrocephalus, probably in the developmental or transitional stage. Progressive clumsiness of his legs necessitated a readmission three months later, at which time urinary incontinence was also noted. Disorientation was more marked than previously. In view of his deterioration, a right ventriculoatrial Pudenz shunt was introduced, some eight months after the onset of symptoms. Despite a functioning shunt, his postoperative mental and neurological status remained unchanged. A steady downhill course marked by fecal and urinary incontinence and debilitating dementia terminated in bronchopneumonia 2½ years after his illness began.

Autopsy Findings: Hypertensive cardiomegaly and severe nephrosclerosis reflected the long-standing systemic hypertension. The brain, weighing 1200 grams, showed minimal parasagittal thickening of the leptomeninges, moderate patchy atherosclerosis of the circle of Willis, mild dilatation of the lateral ventricles, and no gross atrophy of the cortical ribbon. Numerous tiny cystic infarcts were seen in the thalamus bilaterally. Microscopically, moderate concentric hypertrophy of the walls of small arteries and some fibrinoid necrosis of arterioles were accompanied by multiple old perivascular infarcts — "lacunes" (Fisher, 1965; 1969), in the lentiform nuclei, thalamus, subcortical white matter of frontal and temporal lobes, basis pontis, and cerebellar white matter. No senile plaques or neurofibrillary tangles were seen in sections of frontal cortex. Rose's h_2 field of both Ammon's horns revealed a few miniscule old infarcts with focal neuronal depletion and mild gliosis. With routine histological sampling, only an occasional pyramidal neuron in the hippocampi demonstrated Alzheimer's neurofibrillary degeneration (Alzheimer, 1907). The neuropathology was essentially that of hypertensive cerebrovascular disease.

The second patient, a 70 year-old retail clerk (Patient No. 22), was first seen at age 64, with a seven-month history of increasing difficulty with recent memory. He also complained of dizzy spells with transient blurring of vision, slurred speech, and falling to the floor, precipitated by sudden movements of the head or by quickly standing up. His failing memory and brain-stem symptoms were initially suggestive of cerebrovascular insufficiency. B.P. was 140/90. Neurological examination showed only the defect in mentation, but upon re-admission three months later this had worsened to the extent that his overall I.Q. was 64. Aortic arch angiogram showed no atheroma in the extracranial portions of the four cerebral arteries. Pneumoencephalogram revealed moderate dilatation of the ventricles, some air in the Sylvian fissures, and no air over the hemispheres. The RHISA scan by

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lumbar subarachnoid injection showed reflux of CSF into the ventricles, but no activity over the convexities. EEG was non-contributory. A right ventriculoatrial Pudenz shunt was installed some ten months after the onset of his trouble. The intraoperative ventricular pressure, although not measured, was said not to be significantly elevated. Despite the shunt's functioning well post-operatively, there was no appreciable improvement. Two years later, with the shunt still working well, he exhibited inability to dial the telephone, difficulty writing, shaving and dressing himself, and he frequently wandered away from home. He was severely disoriented to time and place and showed some motor inco-ordination. In the last four years of life, he deteriorated further, with frequent falls when walking about the hospital ward, gross mental confusion, profound dementia, and incontinence. He died of bronchopneumonia and ischemic heart disease a little more than six years after the onset of his disease.

Autopsy Findings: The heart, kidneys and other viscera showed no definite evidence of systemic hypertension. The 1200-gram brain had only very mild, patchy atherosclerosis of the circle of Willis, minimal fibrosis of the parasagittal leptomeninges, no cortical atrophy, no dilatation of the ventricular system, and no other gross changes. Microscopically there were large numbers of senile plaques in the cortex of all cerebral lobes bilaterally, and in the mamillary bodies. The senile plaques were especially numerous in the hippocampi, where many neurons contained neurofibrillary tangles, and where granulovacuolar degeneration of Simchowicz (Tomlinson and Kitchener, 1972) and the rod-like bodies of Hirano (Hirano et al, 1968) were also prominent features. Tangles were not seen other than in the pyramidal layer of the hippocampi. A few small arteries and arterioles in the leptomeninges and superficial cortex of frontal, parietal, temporal and occipital lobes demonstrated mild focal hyaline hypertrophy of the media and intimal thickening due to delicate fibrous tissue (sometimes suggesting a "lumen within a lumen"), consistent with the changes in pial vessels described in watershed (marginal) zones following periods of systemic hypotension (Romanul and Abramowicz, 1964). The patient had experienced severe chest pain six months before death, and an old myocardial infarct was confirmed at necropsy.

Sections of basal ganglia showed a mild degree of hyaline arteriolar sclerosis, mainly in each putamen and globus pallidus. Mild widening of perivascular spaces with rarefaction of the neuropil was accompanied by a few foci of astrogliosis and hemosiderin-laden macrophages; and in the head of the right caudate nucleus a single, slit-shaped old infarct was found.

The neuropathological picture was thus not specific, but some features characteristic of both Alzheimer's disease and hypertensive vasculopathy were noted.

The third patient, a 78 year-old retired telegrapher (Patient No. 23), was said to have been psychoneurotic for about 40 years. At age 70 he began to suffer from progressive memory loss, and three years later was grossly disoriented to time and place, exhibiting severe ataxia of gait and urinary incontinence. RHISA scan of lumbar CSF showed retrograde flow into the ventricles and no evidence of normal absorption near the superior sagittal sinus. Pneumoencephalography revealed considerable dilatation of the 4th ventricle, aqueduct, 3rd and lateral ventricles, including the temporal horns. The basal cisterns were enlarged but no air could be seen in the sulci over the convexities. EEG showed non-localizing high voltage, irregular slow waves. A ventriculoatrial shunt introduced four years after the onset of his disease failed to modify the clinical picture. Due to temporary cessation of function five weeks post-operatively, the shunt was revised to a ventriculoperitoneal connection; but despite its patency thereafter he remained totally demented, incontinent and bed-ridden, expiring of bronchopneumonia eight years after his illness began.

Autopsy Findings: Adenocarcinoma confined to the prostate was also present. The brain, weighing only 960 grams, was covered on the left by a thin (3 mm.) fibrous chronic subdural hematoma, possibly the result of a war injury sustained 55 years before death. It did not compress or distort the subjacent cerebrum in any way. The parasagittal leptomeninges were minimally fibrotic. The shunt tube was in place through the right occipital lobe. The circle of Willis was not remarkable.

The narrowed cortical gyri and widened sulci seen from the exterior correlated with a moderate degree of atrophy of the entire cortical ribbon on coronal sections, which also revealed a moderately severe dilatation of the lateral ventricles affecting to a lesser extent the third ventricle, though not the aqueduct or the fourth ventricle. A small old cystic infarct was seen in the left parietal lobe.

Microscopic evidence of two processes was found. Large numbers of senile plaques and neurofibrillary tangles in the hippocampi were accompanied by many neurons with granulovacuolar degeneration and many Hirano bodies. Senile plaques were abundant in frontal, temporal and parietal cortex as well, and in the mamillary bodies. Modest numbers of tangles were seen in middle frontal and cingulate gyri and in inferior temporal gyri. The frontal cortex exhibited considerable neuronal fall-out and gliosis, especially in deeper laminae.

In addition, however, the basal ganglia showed moderately severe onion-skin hypertrophy of small arteries and severe hyaline arteriolosclerosis, especially in each putamen and globus pallidus, where multiple old infarcts (often with hemosiderophages) and widened perivascular spaces indicated a lacunar state. Although vessels in other cerebral regions were not severely affected, occasional microscopic old infarcts were seen in both Ammon's horns and in multiple sites in the subcortical white matter of frontal and parietal lobes; and severe

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arteriolosclerosis in the basis pontis was accompanied by similar old microinfarctions.

Thus, gross and histological features of Alzheimer's disease were present in a brain which also manifested hypertensive cerebrovascular pathology. The severe arterial nephrosclerosis at autopsy was consistent with the latter, although only a mildly elevated blood pressure had been recorded clinically.

The fourth patient, a 57 year-old housewife (Patient No. 24), began to have spells of weakness, lightheadedness and blurring of vision a few times per month, at age 49. In the next 3 years her husband noted some alteration of her personality and a shortening memory span. She had been a good bridge player, but increasing forgetfulness rendered her unable to play. At age 52 an episode of sudden severe pain in the left eye and temple was accompanied by diplopia. An ophthalmologist consulted for the persistent headache noted left lateral rectus palsy, mild left ptosis and slight miosis of the left pupil. Blood pressure was 130/75. Lumbar puncture four days later revealed an opening pressure of 120 mm. and normal CSF. Bilateral carotid angiography showed no berry aneurysms, but a "small loop of vessels" was noted in the region of the anterior communicating artery, in an oblique view of the left carotid injection. Pertechnitate brain scan was normal. Diabetes mellitus was diagnosed with glucose tolerance testing, and she was discharged on Tolbutamide. Her impairment of memory worsened gradually, so that by age 57 she exhibited disorientation to time and place, difficulty with simple commands, dyscalculia and dysgraphia, and a dressing apraxia. Gait was slow and slightly wide-based. The initial clinical impression was Alzheimer's disease. However, pneumoencephalography revealed not only moderate dilatation of the lateral ventricles and the 3rd ventricle with considerable air in widened frontal sulci (indicative of cortical atrophy) but also very little air passing over the vertex despite a considerable amount in the Sylvian fissures, suggesting "low-pressure" communicating hydrocephalus. The RHISA scan by lumbar injection showed reflux of CSF into the lateral ventricles but no activity over the convexities. A brain biopsy was performed through a right frontal burr hole, and a pressure transducer was installed in the right lateral ventricle. Histological examination of the biopsy showed fibrous thickening of the arachnoid; and many senile plaques and neurofibrillary tangles in the cortex, "consistent with Alzheimer's disease". Although a 48-hour telemetric recording of the intraventricular pressure did not show sustained Lundgren waves, repeated short spikes of raised pressure (up to 25 mm. Hg.) were noted, especially during sleep. With these changes and the air encephlographic and RHISA studies indicating some features of NPH, a ventriculoperitoneal shunt (Hockheim type) was installed. Despite excellent flow through the shunt system post-operatively, the patient showed no neurological improvement, became incontinent of urine and feces, and died of bronchopneumonia one month later, some eight years after the onset of her dementia.

Autopsy Findings: The brain was not atrophic, weighing 1275 grams. A mild fibrous thickening of the leptomeninges affected not only the parasagittal regions but extended out laterally over the convexities to the temporal lobes. The meninges over the Sylvian fissures were also fibrotic, but the basal meninges and outlet foramina of the 4th ventricle were normal. The vessels of the circle of Willis showed neither atheroma or berry aneurysms. The lateral ventricles were mildly dilated; the remainder of the ventricular system was grossly normal. A small vascular malformation was discovered occupying the most anterior 1.5 cm. of the left temporal lobe.

Microscopically, large numbers of senile plaques and many Hirano bodies were present in the cortex of both hippocampi, where many neurons exhibited neurofibrillary tangles of Alzheimer and Simchowicz's granulovacuolar degeneration. Focal neuronal loss was accompanied by extensive astrocytosis. Senile plaques and/or neurofibrillary tangles were also noted in mamillary bodies, posterior hypothalamus, superior and middle frontal gyri, middle and inferior temporal gyri, and parietal and occipital cortex. A neurofibrillary tangle was also seen in each locus ceruleus. The malformation of the left temporal pole proved to be a capillary telangiectasis involving cortex and subcortical white matter.

A mild subacute leptomeningitis, ventriculitis and ependymitis, correlating with post-mortem culture of Staphylococcal organisms from the meninges, was attributable to the shunt catheter. There was no evidence of cerebral arteriolar disease or of multiple old infarctions.

In summary, the biopsy diagnosis of Alzheimer's disease seemed appropriate (despite the normal brain weight); but it also appeared possible that a degree of leptomeningeal fibrosis, perhaps secondary to a minor episode of bleeding years earlier from a small vascular malformation, had disturbed CSF flow, resulting in at least some clinical features of "normal pressure" hydrocephalus.

The fifth patient, the only one who responded to shunting (Patient No. 20), was a 63 year-old foreman who despite therapy for systemic hypertension had blood pressures of up to 240/120 and electrocardiographic evidence of left ventricular hypertrophy for at least the last six years of life. About two years before his demise, a transient right hemiplegia and aphasia had been noted. While hospitalized for abdominal pain and depression nine months before death, he exhibited early signs of dementia, difficulty with gait, and some urinary and occasionally fecal incontinence. Pertechnitate brain scan was normal; EEG showed poorly localized excessive slow-wave activity. Re-admission for congestive heart failure three months later revealed poor orientation for dates, poor knowledge of recent events, inability to recall statements a few minutes later, moderate dyscalculia, and a wide-based apractic gait. There was a

mild hypertonic hyperreflexia in the right limbs. Lumbar puncture, which provided normal CSF, had an opening pressure of 120 mm. The RHISA CSF study showed some early and sustained reflux into the ventricles; but also good activity over the convexities in the later films, with a normal decline in count rate. This mixed picture suggested an "early phase" of NPH. Air study showed symmetrical dilatation of the lateral ventricles, particularly their frontal horns; the third and fourth ventricle and the basal cisterns were normal. Air passing over the surface of the hemispheres reached their midportions, but not the vertex. Sulci were not enlarged. EEG showed more diffuse theta activity, with deterioration since the previous tracing three months before.

The diagnosis was "adult communicating hydrocephalus without consistently elevated intracranial pressure"; and a ventriculoperitoneal Pudenz shunt was therefore introduced, approximately 6 months after his dementia had begun. Within 3 days of surgery he was mentally brighter, knew the date and place, did serial 7's competently, and had an improved gait, although noctural urinary incontinence was still present. Despite post-operative cardiac and renal problems he was discharged home 3 weeks after shunting, no longer incontinent of urine, able to walk well without support, and with considerably improved mental status. Recurrent cardiac and renal failure forced a final readmission soon thereafter, though his neurological improvement persisted, and he died in pulmonary edema some 9 months after the onset of his neurological syndrome.

Autopsy Findings: Hypertensive cardiomegaly (450 grams) and shrunken kidneys (90 grams each) with severe arterial and arteriolar nephrosclerosis confirmed the presence of long-standing systemic hypertension. The 1335-gram brain showed a mild leptomeningeal fibrosis which affected not only the parasagittal regions but extended medially into the interhemispheric fissure and laterally over the convexities as far as the temporal lobes. The circle of Willis showed only mild patchy atherosclerosis. As in the four previous cases, the basal leptomeninges and outflow foramina from the fourth ventricle were normal. The ventricular system was not enlarged, and there was no cortical atrophy. The shunt tube was in place through the right occipital lobe. A small old infarct was seen in the right putamen; and another slightly larger in the left basis pontis, explaining the right hemiparesis two years before death.

Microscopically, there were no degenerative changes in the cortex except for a rare senile plaque in frontal, temporal and occipital lobes, and a very rare neurofibrillary tangle in the hippocampi. An occasional miniscule focus of neuronal loss and reactive gliosis was noted in Ammon's horns, and in the left occipital cortex. The basal ganglia were normal. A few small arteries in the thalamus bilaterally, occluded by old embolic material (with cholesterol clefts), were situated next to old microscopic infarcts containing a few residual hemosiderin-filled histiocytes.

The obliteration of portions of the subarachnoid space frontally by the mild fibrosis of leptomeninges was patchy, and no old blood pigment or inflammatory cells were observed to account for the reaction.

The neuropathology was therefore non-specific, and no definite diagnosis of either Alzheimer's disease or of frank hypertensive cerebral vasculopathy could be substantiated morphologically.

Morphometric Methods

Neither the gross or the microscopic changes found on routine neuropathological examination provided a satisfactory explanation for the striking difference in response to shunting between the fifth patient and the other four, although the second, third, and fourth patients did have considerable numbers of hippocampal plaques and tangles. The significance of leptomeningeal fibrosis, somewhat more widepsread in the last two patients, was also unclear. Furthermore, the precise mechanism for dementia was never apparent; a dilated ventricular system per se is unlikely, since shunting frequently returns the size of enlarged ventricles to normal without relieving the mental incapacitation of patients with NPH. Because more detailed quantitative assessment of the (post-mortem) severity of neurofibrillary tangle formation in mesial temporal neurons has recently shown a strong correlation with the dementia of Alzheimer's disease (Ball, in press), morphometric analysis was applied to these five brains as well.

After fixation by suspension in formalin for two weeks, the brainstem and cerebellum were removed and on each side the entire mesial temporal lobe cut sequentially in the coronal plane was blocked for serial 6-μ thick paraffin sections. The area to be screened was outlined on the middle section of each tissue block stained with Congo red-gallocyanin, using ink on the coverslip. The cortical regions examined included Ammon's horn, the prosubiculum, subiculum and presubiculum of the hippocampal formation, and the parahippocampal gyrus laterally to the collateral sulcus. Details of the method are discussed in a previous paper (Ball, in press). No tangles were ever seen in neurons of the dentate gyrus.

The entire area within the inked border was scanned in step-wise fashion using a Wild M501 microscope with a semi-automated (scanning) mechanical stage, at a 200X magnification, with a square ocular (Weibel) graticule. A total of 77,784 microscopic fields were examined in these five cases. With polarized light from crossed Nicol prisms, and a lambda interference filter, Alzheimer tangles exhibit a bright congophilic birefringence and an anomalous dichroism, appearing brilliant yellow-green against a faint blue-orange background (Stokes and Trickey, 1973). It has already been shown that the nucleolar size, and therefore probably the metabolic rate, of a tangle-bearing nerve cell is significantly less than in adjacent uninvolved neurons (Dayan and Ball, 1973). The number of neurons

TABLE 1

Degree of Neurofibrillary Degeneration in Temporal Cortex

Case	Sex	Age	RAW TANGLE INDEX			ADJUSTED TANGLE INDEX			Fixed Brain Weight (grams)
			Left	Right	Both (Total)	Left	Right	Both (Average)	
1	F	47	25	11	36	4.65	1.72	3.19	1000
2	M	52	22	63	85	2.84	6.31	4.58	1270
3	M	53	1	4	5	0.10	0.43	0.27	1430
4	F	56	3	4	7	0.44	0.59	0.52	1130
5	F	59	1	9	10	0.13	1.29	0.71	1300
6	F	60	15	9	24	2.28	1.24	1.76	1170
7	M	63	63	61	124	6.46	6.37	6.42	1330
8	M	67	2	1	3	0.33	0.11	0.22	1350
9	F	68	22	25	47	2.29	2.53	2.41	1250
10	M	69	68	98	166	7.75	12.65	10.20	1250
11	M	70	39	26	65	5.26	3.18	4.22	1190
12	M	76	81	26	107	9.79	3.27	6.53	1000
13	M	76	21	16	37	2.67	1.92	2.30	1380
14	M	76	4	4	8	0.47	0.39	0.43	1310
15	M	77	44	29	71	6.89	3.82	5.36	1530
16	F	81	35	52	87	7.58	12.78	10.18	1020
17	M	82	29	15	44	4.75	2.17	3.46	1230
18	F	83	69	79	148	10.24	8.95	9.60	1250
19	M	89	49	75	124	8.28	12.16	10.22	1040
20	M	63	20	18	38	2.87	2.68	2.77	1335
21	M	78	183	130	313	19.94	17.81	18.88	1270
22	M	70	416	438	854	77.32	77.94	77.63	1170
23	M	78	455	470	925	112.35	98.74	105.55	960
24	F	57	1021	785	1806	171.17	120.44	145.80	1275

the nuclei and nucleoli of which were well visualized, and in which a neurofibrillary tangle was present in the perikaryon was thus recorded for each slide. The total for all slides from both temporal lobes gave each case a "Raw Tangle Index" (Table 1).

The square area of grey matter screened was determined on photographic enlargements of a matched hematoxylin-eosin-Luxol fast blue-stained slide of each middle section (cortex and white matter cannot be well differentiated on Congo red-gallocyanin stains), employing a digitizing device linked to a Hewlett-Packard calculator. As the true thickness of each section was known (5.85 μ), the number of tangle-bearing neurons *per cubic millimeter of cortex* could be calculated for each mesial temporal lobe. The average of both sides provided an "Adjusted Tangle Index" for each case (Table 1).

Nineteen control brains were also examined, from patients aged 47 to 89 years (mean 68.6), neurologically normal and mentally sound according to detailed clinical information. Their ages did not differ significantly from those of the NPH patients ($t = 0.13$, $p > 0.1$). No significant neuropathological changes were found in these brains at autopsy (Ball, in press).

RESULTS

When the Adjusted Tangle Index of the nineteen control cases was plotted graphically against the age of each patient, a significant linear regression line could be shown (Figure 1). The hatched area in Figure 1 represents ± two Standard Deviations from this best regression line. The correlation coefficient r_{df17} is 0.55, statistically significant at the 0.05 level. In mentally normal controls, the degree of neurofibrillary tangle formation in mesial temporal cortex thus correlates well with age, rising very gradually with increasing age.

The Adjusted Tangle Index of Patient No. 20, the normal pressure hydrocephalic who did improve after shunting, was 2.77 (Table 1); this density of tangle formation falls almost exactly on the regression line for normals of similar age (Figure 1). The Adjusted Tangle Indices of the four patients not responding, Patients No. 21, 22, 23 and 24, were 18.88, 77.63, 105.55 and 145.80 respectively (Table 1); and they plot on the graph at levels between four and seventy times greater than controls of similar age (Figure 1).

The density of tangle-formation in the five patients with NPH was then compared with (a) the duration of their dementia before shunting; and (b) the total length of their dementia from onset to death (Table 2). The rank correlation coefficient r_s between the Adjusted Index and either parameter is +1.0. By the null hypothesis, both of these are thus statistically significant correlations at the 0.05 level. In other words, the probability that the increasing tangle indices would rank in the same order as the increasing periods of dementia (either pre-shunt or total) merely by chance is less than 1 in 20.

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TABLE 2

Comparison of Tangle Density and Duration of Dementia

Patient	Age	Adjusted Tangle Index	Duration of Dementia Before Shunting	Total Duration of Dementia
	(years)	(tangles/cu. mm. grey)	(months)	(months)
#20*	63	2.77	6	9
#21	78	18.88	8	30
#22	70	77.63	10	76
23	78	105.55	48	96
24	57	145.80	95	96

(*responded to shunting)

If the degree of tangle formation were a reflection of the length of the dementing process, then the tangle index at autopsy might be expected to correlate quantitatively with the total length of history. While Tomlinson's laboratory (Blessed et al, 1968) has shown a positive correlation between the severity of histological changes and the degree of dementia measured clinically, that report did not mention the total duration of dementia. A negative correlation was shown between the dementia test scores and the actual or the expected period of survival after diagnosis; but there was no reference to any direct correlation between length of dementing history and degree of histological change. In the present study such a positive correlation can be well demonstrated by the best linear regression line between Adjusted Index and total duration of dementia in months (Figure 2), which has a correlation coefficient r_{df3} of 0.96 ($p < 0.02$). The degree of neurofibrillary degeneration in the mesial temporal cortex thus exhibits a remarkably close relationship with the length of the dementing process.

DISCUSSION

In a recent study of 25 patients with NPH (Jacobs et al, 1976), the post-shunt condition was classified as "complete improvement", "moderate improvement" or "no improvement". The authors claim the improved patients' clinical signs (dementia, motor dysfunction, incontinence) had been present for less time than those who did poorly ($p < 0.01$). Those showing no change had been ill for an average of 40 months (range, 6 to 120 months); those with moderate improvement, 21 months (1 to 39); those with complete improvement, only 14 months (3 to 36). No pathogenetic mechanism was proposed to account for this correlation. No relationship existed between either the corpus callosum angle or the cerebral mantle thickness on pneumoencephalography and either the surgical outcome or the duration of illness. Previous data (Ball, in press) from the brains of eight patients showing organic dementia of the Alzheimer disease type — both presenile and senile (McMenemey, 1971) have indicated that the number of neurons bearing a neurofibrillary tangle of Alzheimer, expressed per cubic millimetre of mesial temporal cortex, is appreciably greater (from six to forty times larger) than in serially sectioned hippocampi of age-matched normal brains (Figure 3; Ball, in press). Since four of the five patients with NPH in the present report who failed to respond to technically successful shunting had a similar striking increase in neurofibrillary degeneration in their mesial temporal lobes, whereas the one man who improved dramatically after shunt had a normal, minimal degree of tangle-formation (Figure 1), it is reasonable to speculate whether the magnitude of neurofibrillary change could explain the difference in response to therapy. Earnest et al (1974) also remarked that their 66 year-old man who did respond to shunting showed only a "few fibril-

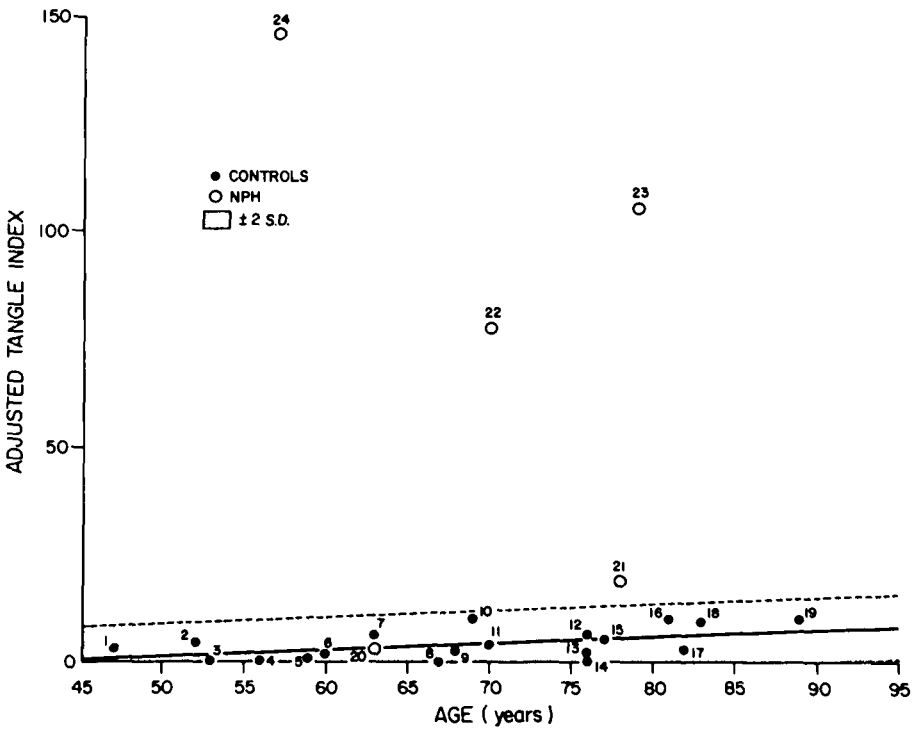

Figure 1—Relationship between Adjusted Tangle Index (number of tangle-bearing neurons per cubic millimeter of mesial temporal cortex) and patients' age in years. The best linear regression line for the nineteen control brains (closed circles) has a significant correlation coefficient ($r = 0.55$, $p < 0.05$). Patients No. 20 to 24 (open circles) had "Normal Pressure" Hydrocephalus: No. 20 responded to shunting; Nos. 21, 22, 23 and 24 showed no improvement.

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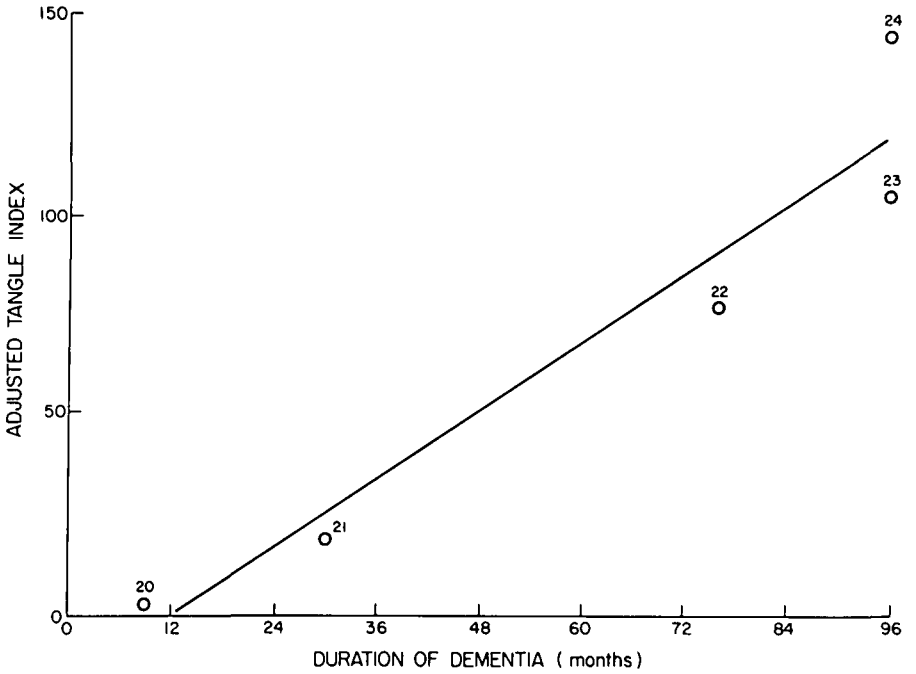

Figure 2—Relationship between Adjusted Tangle Index and duration of dementia in NPH (in months). A striking linear correlation exists ($r = 0.96$, $p < 0.02$).

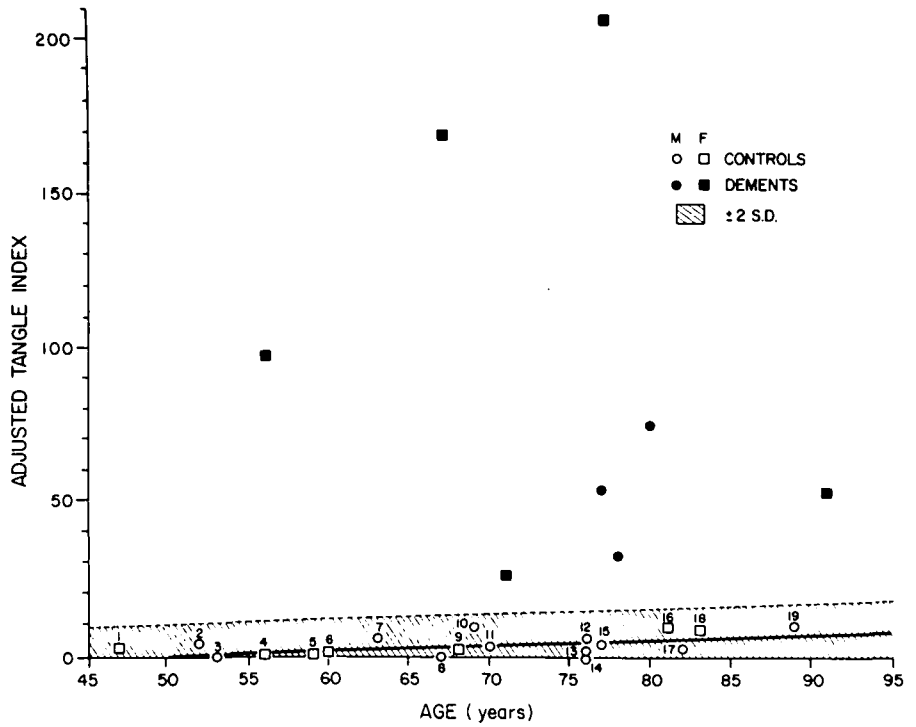

Figure 3—Comparison of Adjusted Tangle Index in nineteen control patients (open symbols), and in eight demented patients (closed symbols) whose brains demonstrated Alzheimer's disease. Males, circles; females, squares. (From Ball, in press). The density of tangles in Alzheimer's dementia is similar to that noted in the four unimproved cases of NPH in Figure 1.

lary tangles" in the hippocampus.

Furthermore, if as Figure 2 suggests, the intensity of tangle-formation might be a function of duration of the dementia, then the somewhat shorter period before shunting perhaps would explain the excellent response of our fifth case (Patient No. 20) — who was operated upon within six months of the commencement of his dementia. The irreversibility of dementia in the others might reflect their much more severe histopathological state. Results of shunting in Jarpe's series (1970) hinted at the same phenomenon: patients with "a defined arachnoiditis" rarely failed to benefit, while those with "presenile dementia" rarely improved.

It seems unlikely that multiple small infarcts would adequately explain the lack of response in our four patients. While numerous old infarctions were noted in cases No. 21, 22 and 23, the aggregate volume of infarcted tissue in two of these brains (No. 21 and 22) almost certainly did not total 50 cu. cm., an amount usually exceeded in dementia of the so-called arteriosclerotic (Tomlinson et al, 1970) or "multi-infarct" variety (Hachinski et al, 1974). Although multiple infarcts might have contributed to the clinical presentation in Case No. 23, the pathological changes typical of Alzheimer's disease were also found. No infarcts at all were seen in the brain of Case No. 24, who also failed to respond. Finally, numerous old infarcts not inconsistent with a mild lacunar state (Fisher, 1965; 1969) were seen in Patient No. 20, in spite of which he did improve dramatically.

Hypertension would also not readily account for the lack of response in the four cases. Earnest et al (1974), drawing attention to the association of lacunes and NPH, have speculated that many infarcts could reduce tissue bulk or tensile strength, permitting ventricular dilatation in the face of the increased CSF pulse pressure of hypertension. Only one of our four unimproved cases had significant systemic hypertension; and by contrast, the improved patient also was severely hypertensive.

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From our observations, it may be asked whether in some individuals with clinical evidence of a NPH syndrome, an as yet undefined pathogenetic process — ? "Alzheimerization" — can lead, if severe enough and/or long-lasting enough, to histological degeneration of the cerebral cortex. Preliminary data from our laboratory suggest that cellular alterations identical to, though somewhat less severe than those quantitated in this study in the mesial temporal lobes, are also occuring in numerous other portions of the cortical mantle. The resultant degree of generalized neuronal damage, as reflected by the amount of neurofibrillary change in the mesial temporal cortex, might determine whether alteration of CSF dynamics by shunting could still reverse the dementing process. It is not known why the abnormal CSF flow is associated with neuronal degeneration, although Katzman (1976) has recently drawn attention to this association in his speculation that the possible bulk removal of CSF by pial vasculature might be altered in the presence of meningeal fibrosis in Alzheimer's disease. Whatever the explanation, if this small series proves representative, the best hope of success for treating the dementia of NPH would lie in earliest possible diagnosis.

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