PARKINSONISM-DEMENTIA COMPLEX, AN ENDEMIC DISEASE ON THE ISLAND OF GUAM

II.—PATHOLOGICAL FEATURES

BY

ASAO HIRANO1, NATHAN MALAMUD2 AND LEONARD T. KURLAND3

INTRODUCTION

In the course of the investigations of the phenomenal incidence of amyotrophic lateral sclerosis on the Western Pacific Island of Guam, numerous patients with a syndrome of presenile dementia, features of Parkinsonism and, often, motor neurone involvement, have been observed. This syndrome, found exclusively in the indigenous Chamorro population, usually develops insidiously in the fifth to seventh decades and has an average duration of about four years from the onset of symptoms until death. This syndrome accounts for about 7 per cent of deaths among adult Chamorros. The possible relationship of this disorder to the amyotrophic lateral sclerosis of the Chamorros has been discussed by Hirano, Kurland, Krooth and Lessell in a companion paper in this series.

The neuropathological characteristics of the cases to be described were first observed by one of us (N. M.) in the course of examinations of specimens from Guam a few years ago. Stimulated by these findings, a concerted effort was made by one of the authors (A. H.) to obtain autopsies on all Guamanians dying of neurological disease. During a ten-month period, from August 1959 to June 1960, 11 of the 17 cases of Parkinsonism with presenile dementia reported here were autopsied.

There has been no report on the neuropathology of this disease as it occurs on Guam. The main purpose of this paper is to present the pertinent neuropathological features of the 17 necropsied cases. These are summarized in Tables I to III. Detailed reports are given for 2 cases and brief, additional remarks are made on the other 15 cases.

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Table I.—Clinical Data on Parkinsonism-Dementia Complex Among the Chamorros on Guam

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Year of onset</th>
<th>Date of death</th>
<th>Age at death</th>
<th>Approximate duration in years</th>
<th>Evidence of amyotrophic lateral sclerosis</th>
<th>Additional clinical diagnosis</th>
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<td>M</td>
<td>1954</td>
<td>Nov. 12, 1959</td>
<td>61</td>
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<td>Left eye was enucleated because of trauma.</td>
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<tr>
<td>2</td>
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<td>1953</td>
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<td>0</td>
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<tr>
<td>4</td>
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<td></td>
</tr>
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<td>5</td>
<td>M</td>
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</tr>
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<td>6</td>
<td>M</td>
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<td>59</td>
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<tr>
<td>11</td>
<td>M</td>
<td>1956</td>
<td>June 26, 1958</td>
<td>52</td>
<td>2</td>
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<td>Rheumatic heart disease</td>
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<td>12</td>
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<td>1955</td>
<td>Feb. 16, 1958</td>
<td>52</td>
<td>3</td>
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<td>13</td>
<td>F</td>
<td>1958</td>
<td>April 30, 1960</td>
<td>48</td>
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<td>14</td>
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<td>15</td>
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<td>May 11, 1960</td>
<td>59</td>
<td>4</td>
<td>+</td>
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</tr>
<tr>
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<td>M</td>
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<td>May 24, 1960</td>
<td>53</td>
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<td>17</td>
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<td>June 25, 1960</td>
<td>54</td>
<td>6</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*Diagnosis was first made on this date. The date of actual onset was not available in these cases.

Case Reports

Case 1.—A Chamorro man gave a history of progressive physical slowness and mental deterioration dating back to 1954 when, at the age of 56 years, he was retired from his government job. These clinical features were noted during hospitalizations at the Guam Memorial Hospital for phlebitis of the right leg in June 1956, and for gastrointestinal symptoms in March 1957. The patient was first seen at the Guam Neurological Research Center on July 14, 1957. At that time, he complained of forgetfulness and of being unable to recognize friends whom he had not seen recently. Memory for both recent and past events was poor. He was vaguely oriented as to time and place, and his recall of general information was poor. He walked leaning forward without moving his arms. His face was mask-like. There was generalized weakness, but no obvious muscle atrophy. There was plastic rigidity with cogwheel resistance of the extremities, and marked slowness when changing his posture or position. No tremor was noted. Muscle stretch reflexes were hyperactive and equal bilaterally, and no definite pathological reflexes were elicited. The cranial nerves were intact, and the sensory examination was normal. His illness, diagnosed as Parkinsonism with mental deterioration, progressed gradually. Extensive laboratory studies including blood serology, chemistry, hematology, urinalysis and radiological investigations were within
normal limits. There was no family history of amyotrophic lateral sclerosis or Parkinsonism.

On examination in his home on September 16, 1959, he was emaciated and chair-ridden. He was completely silent, somewhat confused and apathetic throughout the examination, and it was almost impossible to communicate with him even in his native language. He seemed unable to comprehend or to follow simple commands during the examination. His mouth was tightly shut, so that his family had difficulty in feeding him. His jaw-jerk was hyperactive, and a snout reflex was present. Eye movements and pupillary responses were normal. There was marked rigidity, but no tremor in the extremities. Muscle stretch reflexes were hyperactive and equal bilaterally; there was still no Babinski sign. Focal muscular atrophy and fasciculations were absent.

When he was observed again on October 5, 1959, he was bedridden, and it was almost impossible to open his mouth to feed him. He deteriorated rapidly and expired on November 12, 1959.

Post-mortem examination.—The general autopsy showed bilateral hypostatic pneumonia and infected decubiti over the sacral area.

Macroscopic observations.—The unfixed brain weighed 1,064 grammes. The total protein of cerebrospinal fluid taken from the cisterna magna at the time of autopsy was 39 mg. per cent. The dura mater and superior longitudinal sinus were intact. The cerebral hemispheres were well developed, symmetrical and covered by slightly milky and thickened leptomeninges. The cerebral gyri were narrowed and the sulci were widened in the fronto-temporal areas (fig. 1A, Plate LXXXIII). The blood vessels at the base of the brain formed a complete circle of Willis. Both posterior cerebral arteries arose from the internal carotid arteries. The right anterior cerebral artery was very small between the internal carotid and anterior communicating arteries. In contrast, the left anterior cerebral artery was very large, and it supplied the anterior communicating artery and major distal portion of the anterior cerebral arteries bilaterally. The walls of the major arteries were thin and elastic and contained few atheromatous plaques. The cranial nerves appeared normal. Coronal sections of the hemispheres revealed well-demarcated grey and white matter. The cortex in the frontal and temporal lobes appeared to be narrowed. The ventricular system was symmetrically dilated (fig. 1B). There was gross atrophy of the globus pallidus bilaterally. The Sylvian fissure was widened due to atrophy of the frontal and temporal gyri, as well as the insula. The substantia nigra lacked its normal dark appearance (fig. 1C). The locus ceruleus was not identified; otherwise, transverse sections of the cerebellum and brain-stem were unremarkable.

Microscopic observations.—The cerebral cortex was covered by slightly thickened and fibrotic leptomeninges without acute inflammatory changes.

The cortical architecture was relatively well preserved in most areas with the exception of the temporal cortex which presented disorganization of its laminar arrangement. Scattered throughout the frontal and temporal cortex were large numbers of ganglion cells which showed alterations. There was loss of Nissl substance in some of the neurones and accumulation of intracytoplasmic lipid granules in others. The most prominent features were abundant neurofibrillary changes (fig. 2A) and intracytoplasmic granulovacuolar bodies (fig. 2B). There were only occasional neuronophages, sateilitosis and actual disappearance of ganglion cells. These changes were most severe in the temporal lobe, particularly in Sommer's sector and the presubiculum of the hippocampal gyrus. The frontal pole, orbital gyri and cingulate gyri were somewhat more involved than other parts of the frontal lobe. The ganglion cells of the parietal and occipital lobes were much less affected, and the visual cortex was entirely free of neurofibrillary changes and granulovacuolar bodies. There was severe astrocytic gliosis in
PLATE LXXXIII

Fig. 1 (Case 1).—Parkinsonism-dementia complex on Guam. A, Atrophy of frontal lobes. Cerebellar hemispheres are normal. B, Moderate dilatation of frontal horns. C, Loss of pigment in substantia nigra in upper figure as compared with the normal in the lower.

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 2 (Case 1). Sommer's sector. a. Neurofibrillary change 970. b. Nerve cell with granulovacuolar bodies. 970. c. Bielschowsky stain.) e. Hypertrophic astrocytes. 970 (von Braunmühl stain.)
Fig. 3 (Case 2).—A, Mild general atrophy and moderate dilatation of lateral ventricles. A small block of tissue was removed along the third ventricle on right side. B, Loss of pigment in substantia nigra in upper figure as compared with the normal in the lower.

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 4 (Case 2).—Sommer's sector.  A, Argyrophilic Alzheimer's neurofibrillary changes of nerve cells.  × 1,100.  B, Typical condensation of argyrophilic neurofibrils of a pyramidal cell.  × 1,500.  C, Granules in cytoplasm of a pyramidal cell are argyrophilic and surrounded by vacuoles.  × 1,400.  D, Subiculum.  Nerve cells with typical Alzheimer's neurofibrillary changes.  × 150. (A–D; von Braunmühl stain.)

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 5 (Case 3).—Sommer's sector. A, Altered pyramidal cells with typical Alzheimer's neurofibrillary change. $\times 110$. B, Higher magnification of the area illustrated in A (square). $\times 900$. C, Higher magnification of the area illustrated in A (thickly-lined square). $\times 1,070$. (A−C: Bielschowsky stain.)

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
FIG. 6 (Case 3).—Sommer’s sector. A and B, A mass of comparatively weakly argyrophilic neurofibrils. Adjacent neuraxons are thickened and strongly argyrophilic. ×1,300. C, Presubiculum. A pyramidal cell with typical Alzheimer’s neurofibrillary change. ×1,150. D, Subiculum. ×500. (A–D: Bielschowsky stain.)

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 7 (Case 4).—Sommer's sector.  A, Two pyramidal cells with typical Alzheimer's neurofibrillary changes at the lower right corner. A pyramidal cell with a large amount of argyrophilic granular substance in its cytoplasm at the upper left corner. ×490.  
B, An enormously swollen pyramidal cell with a combination of Alzheimer's neurofibrillary change and granulovacuolar bodies. ×1,100.  
C, Two pyramidal cells with granulovacuolar bodies. Tiny argyrophilic granules surrounded by vacuoles are present in cytoplasm. ×1,100.  
D, An atypical plaque with neurofibrillary change and a pyramidal cell with granulovacuolar bodies (arrows). ×1,070.  
E, Pyramidal cell with typical Alzheimer's neurofibrillary change and another with typical granulovacuolar bodies. ×1,070. (A–E: von Braunmühl stain.)
FIG. 8 (Case 8).—Nucleus dorsalis raphes at cranial pons. A, A series of various changes of nerve cells. Arrows mark off ependymal lining cells. ×110. B, Higher magnification of the area illustrated in A (square). Swollen cytoplasm of a nerve cell with eccentric nucleus is filled with thickened neurofibrils and a few deep-green pigmentary granules. ×980. (A–B: Toluidine blue stain.)

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 9 (Case 9).—Symmetrical atrophy and brown pigmentation of the globus pallidus.

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 10 (Case 13).—A–B, Autopsy specimen showing disproportionate size of skull to brain, especially frontal and temporal areas.
Fig. 11 (Case 13).—A, Moderate dilatation of both frontal and temporal horns. 
B, Depigmentation of substantia nigra.

To illustrate article by Asao Hirano, Nathan Malamud and Leonard T. Kurland.
Fig. 14. Parkinsonism-dementia complex on Guam. Typical Alzheimer's neurofibrillary change in pigmented cells of substantia nigra and brain-stem. (Hämatoxylin-eosin stain.)

To illustrate article by Asao Hirano, Nathan Malamud and Leonard J. Kurland
the involved cortex, as well as in the adjacent white matter (fig. 2c). Macrophages were scant and only scattered sudanophilic granules were found free in the cerebral tissue. Reactive microgliosis was commonly observed. Senile plaques were not observed.

The neurofibrillary changes were located primarily in the hypothalamus, amygdaloid nucleus and substantia nigra, and were relatively rare in the basal ganglia and thalamus. Subependymal gliosis was prominent along the third and lateral ventricles. A poverty of ganglion cells in the globus pallidus was associated with severe gliosis. The pigmented zone of the substantia nigra showed severe neuronal loss with scattered neurofibrillary changes in the remaining cells of the medial and cranial portions of this structure. The caudal portion of the substantia nigra showed severe astrocytic gliosis, so extensive that almost its entire structure was replaced by a glial fibrous network. A Sudan stain of this region showed little sudanophilic material. There were no Lewy bodies. The tegmentum of the mid-brain and the periaqueductal area also contained scattered neurofibrillary changes.

In the pons and medulla there was severe cell loss in the locus ceruleus and the dorsal nucleus of the vagus. There were occasional neurofibrillary changes in the cells of the reticular formation, but none in the pontile or inferior olivary nuclei. In the latter, the neurones were filled with lipofuscin. The cerebellum was free of any abnormality. The dentate nucleus contained an excessive accumulation of lipofuscin. In the spinal cord occasional neurofibrillary changes were noted in the small cells of the lateral horn at the cervical and thoracic levels.

There was no evidence of demyelination or inflammatory changes.

Case 2.—At the age of 53 years, this Chamorro farmer developed early signs and symptoms of dementia and a Parkinsonian syndrome with no known antecedent febrile illness. On examination a characteristic Parkinsonian posture and gait were evident. There was a tremor of the hands, but neither the generalized increase in muscle tonus nor the cogwheel rigidity was pronounced. After six years of slowly progressive illness, the patient died of cachexia and hypostatic pneumonia. The patient's mother had died of amyotrophic lateral sclerosis.

Post-mortem examination.—The findings of the general autopsy were severe emaciation, decubiti of the buttocks and sacral area and hypostatic pneumonia.

Macroscopic observations.—The unfixed brain weighed 960 grammes. The major arteries at the base of the brain were thin and elastic, and free of atheromatous plaques. The left vertebral artery was three times larger than that of the right side. There was moderate atrophy of the cerebral cortex in the frontal and temporal lobes bilaterally. Coronal sections of the hemispheres revealed narrowing of the cortex, and moderate dilatation of the ventricular system (fig. 3A). There was bilateral gross atrophy of the globus pallidus. The brain-stem and cerebellum were unremarkable except for the lack of pigmentation of the substantia nigra (fig. 3B) and locus ceruleus bilaterally.

Microscopic observations.—There were severe alterations in the ganglion cells of the frontal and temporal lobes, especially in Sommer's sector and the temporal pole. Many of the neurones showed neurofibrillary changes of varying degree, and in some of the neurones there were also intracytoplasmic granulovacuolar bodies (fig. 4). There was hypertrophic astrocytic gliosis, but inflammatory changes were absent. Macrophages were not found. There were no senile plaques or Pick's globular argyrophilic inclusions observed. A severe degeneration of the globus pallidus was characterized by a paucity of neurones and reactive gliosis, the latter consisting predominantly of glial fibres. The change was bilateral and symmetrical, involving all parts of the pallidum, in contrast to the absence of changes in the adjacent putamen and caudate nuclei. There was equally severe, symmetrical degeneration of the substantia nigra with only scat-
tered islands of pigment-containing neurones remaining, some of the pigment being stored in phagocytes or lying free in the tissue. There was dense reactive gliosis, composed largely of fibres. A more moderate degeneration affected the nuclei of the brain-stem bilaterally; primarily, those of the periaqueductal grey matter and the nucleus pigmentosus. Neurofibrillary changes, with or without accompanying degeneration, were present in the anterior perforating substance, various hypothalamic nuclei, amygdaloid nucleus, and in the tegmentum of the brain-stem, including the degenerated substantia nigra, nucleus pigmentosus, mid-line raphe and dorsal nucleus of the vagus. Neurofibrillary changes were not observed in the visual cortex, pontile nuclei, inferior olivary nucleus, Purkinje cells or dentate nucleus. There was no demyelination of the pyramids or the lateral columns, but a few macrophages containing sudanophilic material were scattered in the vicinity of blood vessels in these areas.

Case 3.—At 47 years of age, this Chamorro male developed symptoms of organic mental disease followed by Parkinsonism. When he died four years later, he was cachectic and had pulmonary tuberculosis. Neuropathological findings were essentially the same as those of the previous 2 cases. The abundant neurofibrillary changes found in this case are illustrated in figs. 5 and 6.

Case 4.—This Chamorro female developed symptoms at 51 years of age and died two years later. The outstanding pathological features were ganglion cell changes with abundant neurofibrillary alterations and intracytoplasmic granulovacuolar bodies; their distribution was similar to that of the previous cases. Fig. 7 shows these changes, together with an atypical plaque which was observed.

Case 5.—At the age of 56 years this man developed dementia and Parkinsonism. The total course of his illness was about two years. There was unusually severe involvement of the substantia nigra and brain-stem and neurofibrillary changes were present throughout the brain, including the usually-spared inferior olive, olfactory bulb and the motor neurones of the brain-stem. Another unusual feature in this case was the rare neurofibrillary changes in the visual cortex. Examination of the circle of Willis disclosed that the posterior communicating vessels were of the same calibre as the posterior cerebral arteries and appeared to arise from the internal carotid vessels. A small branch from each of the posterior cerebral arteries communicated with the basilar artery.

Case 6.—This male patient developed symptoms of Parkinsonism in 1954, but a clinical diagnosis was not made until May 1957. He was also demented and died at the age of 58 years in a state of cachexia on July 23, 1959. He was known to have hypertension (B.P. 190/120–210/140) since 1956. Microscopically, this case showed a particular abundance of cells with neurofibrillary changes; these were most prominent in the substantia nigra, the dorsal motor nucleus of the vagus and the hypothalamic nuclei. In addition, moderately severe athero- and arteriolo-sclerotic changes were evident in the cerebral vessels.

Case 7.—This male patient died at the age of 59 years with a progressive dementia and Parkinsonism picture of uncertain duration. He also had known hypertension which ranged from 166/110 to 210/140. General autopsy showed left ventricular hypertrophy and pulmonary congestion. However, the blood vessels at the base of the brain were almost free of atheromatous plaques. There were severe neuronal changes of the same nature as noted in the preceding cases.

Case 8.—This male patient died at 68 years of age; the duration of his illness was four years. Various changes of nerve cells in the nucleus dorsalis raphes at the cranial pons are illustrated in fig. 8. The Nissl stain demonstrates the swollen cytoplasm of a
nerve cell with an eccentric nucleus which is filled with altered neurofibrils and a few deep-green staining pigmentary granules. Small subacute infarcts were found in the ventral thalamus. Other neuropathological findings were similar to the cases described in detail.

Case 9.—The diagnosis of presenile dementia with Parkinsonism was made in 1956; he died the following year at the age of 52 years. Macroscopically, the most outstanding changes were the symmetrical atrophy and brown pigmentation of the entire globus pallidus (fig. 9) and the substantia nigra. Microscopically, the majority of neurones had disappeared or were absent in these structures; reactive gliosis and some pigment granules in phagocytes and glial cells were present. There were also large round bodies with granular deposits representing some unknown process of degeneration. In the oculomotor nuclei there was a paucity of cells, and of those remaining, some contained neurofibrillary tangles. In spite of this there were no discernible manifestations of ocular disturbance.

Case 10.—At 58 years of age, this man developed symptoms of a slowly progressive dementia with Parkinsonism and died five years later. In this case, neurones with neurofibrillary changes were most numerous in the nuclei of the hypothalamus, the periaqueductal region of the mid-brain, and to a lesser degree in the cerebral cortex.

The following two patients presented clinical features of amyotrophic lateral sclerosis, in addition to dementia and Parkinsonism. Details of the clinical aspects of these cases are included in the report by Hirano, Kurland, Krooth and Lessell.

Case 11.—This Chamorro man died at the age of 52 years after an illness of only two years. General post-mortem examination showed inactive mitral valvulitis of the heart and multiple decubiti. Neuropathological findings: the brain, which weighed 1,000 grammes after formalin fixation, was small and symmetrical and showed no abnormality other than suggestive atrophy of the frontal gyri. There was no evidence of atherosclerosis in the basal arteries. Coronal sections revealed atrophy of the globus pallidus and depigmentation of the substantia nigra. The significant microscopic changes were as follows: (a) Chronic bilateral degeneration, characterized by loss of neurones and replacement gliosis, which was most marked in the substantia nigra and locus caeruleus and more moderate in the globus pallidus and tegmental parts of the brain-stem. There were no Lewy bodies. (b) Degeneration of a severe degree in many areas of the cerebral cortex, characterized by depletion of neurones, active micro- and astroglial reactions, without senile plaques or signs of cerebral vascular disease. The Betz cell region of the cortex appeared to be the least affected. (c) Bilateral demyelination of the pyramidal tracts. (d) Bilateral degeneration of the hypoglossal nuclei and of the anterior horn cells in the spinal cord. (e) Neurofibrillary lesions similar to those described in the foregoing cases were numerous in the hypothalamus and tegmentum of the brain-stem, and moderately severe in the cerebral cortex and other areas.

Case 12.—A Chamorro man who died at the age of 52 years presented initially as an organic mental syndrome with Parkinsonian features, and subsequently developed additional motor neurone signs. On general post-mortem examination there was bilateral pulmonary congestion and oedema and chronic cystitis. The formalin-fixed brain weighed 940 grammes. It was small and symmetrical with a suggestion of atrophy of the frontal gyri. Blood vessels appeared normal. Coronal sections revealed moderately enlarged lateral ventricles, questionable diffuse cortical atrophy, and slight atrophy of the globus pallidus and substantia nigra. The spinal cord was
thinner than normal throughout, and after sectioning, the anterior horns could not be identified. The anterior and lateral fascicles were reduced in size. Microscopically, two types of change were noted: (1) Degeneration of anterior horn cells, most marked in the cervical regions, together with demyelination of the pyramidal tracts and a paucity of Betz cells in the motor cortex. (2) Atrophy with diffuse cerebral changes, characterized by a disappearance of neurones, severe in the substantia nigra and globus pallidus and moderate in the cerebral cortex, hypothalamus and periaqueductal region. There were numerous neurones with neurofibrillary changes of Alzheimer scattered throughout the affected areas.

Cases 13 to 17.—The clinical and pathological features which are included in Tables I to III are essentially similar to those already presented. A brother of Case 14 had died of presenile dementia with Parkinsonism. A brother of Case 17 had died of “Lytico,” the term commonly used by the Chamorro population to refer to amyotrophic lateral sclerosis, the Parkinsonian syndrome, or other progressive paralytic disease. In Case 15 the septum pellucidum was virtually absent, being represented only by rudimentary fibres, in the vicinity of the blood vessels. In this case there was no cerebral substance between the mammillary bodies and the adjacent area, the third ventricle opened widely into the basal cistern.

DISCUSSION

All 17 cases presented in this report have certain neuropathological changes in common. Macroscopically, there is cerebral atrophy, pallidal atrophy and loss of pigmentation in the substantia nigra and locus caeruleus. Microscopically, severe neuronal alterations associated with gliosis are observed in certain areas. The altered ganglion cells show two specific features: Alzheimer's neurofibrillary changes and intracytoplasmic granulovacuolar inclusion bodies. In addition, accumulation of intracytoplasmic lipid granules and other manifestations of nonspecific neuronal degeneration are observed. The loss of neurones is most apparent in the globus pallidus and the substantia nigra. Each of these features will be discussed in detail below:

(1) Cerebral Atrophy

All of the patients presented with a clinical history of progressive dementia which is described in greater detail in the clinical report (Hirano, Kurland, Krooth and Lessell). Although the skull is of normal size, the brain is usually small, and there is a compensatory increase in the quantity of cerebrospinal fluid (figs. 10A and B). The total protein content of this fluid is normal. The weight of the brain ranges from 860 to 1,310 grammes with a mean of 1,039 grammes (Table II). This is appreciably less than the mean weight of European brains which, for ages 51 to 60 years, average 1,338 grammes for males and 1,254 grammes for females (von Braunmühl, 1957). Although only a limited number of adult Chamorro brains in which neurological disease was absent have been examined, their weight falls within the normal range for Europeans.

The question of racial difference of the brain weight is further discounted because of the difference between the actual skull capacity and
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<th>Dilatation of ventricles</th>
<th>Pallidal atrophy</th>
<th>Pallor of substantia nigra</th>
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<td>Minimal</td>
<td>Moderate</td>
<td>Moderate</td>
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<td>+</td>
<td>Hypostatic pneumonia, infected decubiti</td>
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<td>960</td>
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<td>Moderate</td>
<td>Moderate</td>
<td>+</td>
<td>+</td>
<td>Hypostatic pneumonia, emaciation, decubiti</td>
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<td>970</td>
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<td>Minimal</td>
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<td>+</td>
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<td>Minimal</td>
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the volume of the brain at autopsy. Widening of the sulci and narrowing of the gyri are more apparent over the frontal and temporal lobes, whereas the parietal and occipital lobes are relatively well preserved. The cerebral atrophy is always bilateral, but the lobar atrophy characteristic of Pick's disease is not found. On coronal sections the only significant abnormality is minimal to moderate dilatation of the lateral ventricles, particularly in the frontal and temporal horns. However, it is important to note that sectioning the hemispheres in these cases may not show any striking gross abnormality of the cortex or white matter despite severe involvement histologically.

(2) Depigmentation of the Substantia Nigra and Locus Cœruleus; Atrophy of the Globus Pallidus

The substantia nigra lacks its normal black pigmentation, appears pale brown at all levels and seems atrophic bilaterally (figs. 11A and B). Identification of the locus cœruleus is usually impossible on gross examination due to the loss of its black pigmentation. The globus pallidus shows moderate to severe atrophy in all specimens.

(3) Neurofibrillary Changes

These are conspicuous in all cases. They are readily seen with axon stain preparations such as Bielschowsky's and von Braunmühl's. The mildly affected ganglion cells show well-preserved cellular elements such as nucleus, nucleolus, cellular dendrites and cytoplasm with the exception of a single or a few abnormally thickened argyrophilic neurofibrillary filaments in the periphery of the cytoplasm. Other cells contain coarse, thick fibres which coil around the nucleus a few times from the apical dendrite to the base. Still others form a mass of fine tangles of fibres which fills the entire cytoplasm. Generally speaking, this spool-like type stains less intensely than the thick "rope" type. The nucleus is usually deformed and peripherally located, so that the perikaryon assumes a more or less swollen, rounded form. Many of the severely affected ganglion cells are completely replaced by tangles of the fibrillar mass. Frequently, they appear like a torch of fibrils with no other cellular elements remaining, particularly so in the pyramidal cells of the hippocampus.

Malamud, Haymaker and Pinkerton (1950) observed that neurofibrillary changes can also be seen clearly with Nissl or hæmatoxylin-eosin stains of either frozen, paraffin or celloidin-embedded sections. Greenfield and Bosanquet (1953) also demonstrated the fibrils in cases of Parkinsonism with Lendrum's phloxin tartrazine stain, and observed that the fibrils which stained feebly with Congo red demonstrated anisotropism under polarized light.

Ishii (1958) studied the neurofibrillary changes in 10 brains of pre- senile and senile dementia. When Congo red stain was applied, some
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*Only one or two neurofibrillary changes were observed per slide.*
fibrils were stained and doubly refractile, while others were not. Those which stained appeared red with silver impregnation, were positive with periodic acid Schiff (PAS), metachromatic, stable with hyaluronidase and stained with Alcian blue. These staining characteristics were the same as those of acid mucopolysaccharides. The fibrils were positive with coupled tetrazonium reaction, did not alter their colour significantly with dinitrofluorobenzene and performic acid, and were discoloured after benzoyl chloride treatment. These results correspond to the reactions observed in senile plaques. Those fibrils which did not stain with Congo red showed negative reactions to all the above-mentioned stains for mucopolysaccharides. The neurofibrillary changes in our series are also readily observed with haematoxylin-eosin, Nissl, or with Lendrum's phloxin tartrazine stains, but they are non-sudanophilic, non-metachromatic, weakly positive or negative with PAS, stained with Congo red, and doubly refractile when polarized light is applied. There are no typical senile plaques.

The distribution of the altered ganglion cells is remarkable in that they always appear in certain specific parts of the central nervous system in all cases (Table III). The most severely involved area is the pyramidal cell layer of the hippocampus, particularly Sommer's sector, and the presubiculum. The substantia nigra is usually so severely damaged that neuronal loss is the most prominent feature. However, some intraganglionic fibrillary changes are always found in the remaining cells of the craniomedial parts of this structure. The hypothalamus is also severely affected and the mammillary bodies are frequently the site of gliosis. The anterior perforating substance, the substantia innominata, and the amygdaloid nucleus are also intensely involved. The more moderately affected areas are the frontal cortex, especially the cingulate gyrus and frontal pole, the temporal lobe, particularly in its anterior portion, the ganglion cells around the third ventricle and aqueduct of Sylvius, and occasionally around the fourth ventricle. The quadrigeminal plate and third nucleus contain occasional fibrillary changes, as do the tegmentum of the pons and medulla oblongata. The dorsal nucleus of the vagus is more commonly involved than the other motor cranial nuclei. The locus caeruleus shows a severe loss of cells, but neurofibrillary changes are scant. The ganglion cells of the reticular formation present scattered fibrillary changes. The smaller neurones of the olfactory bulb and of the spinal cord show occasional neurofibrillary changes. The visual cortex and the Purkinje cells are free of these changes in most of the cases. The distribution of the involved cells is almost always bilaterally symmetrical (fig. 12). It is of interest to note that the lesions show a predilection for the limbic system. In general, most of the neurofibrillary changes in the cerebral cortex differ in shape from those in...
the hypothalamus, amygdaloid nucleus, substantia nigra and brain-stem (figs. 13, 14).

Alzheimer's neurofibrillary degeneration of the ganglion cells is an essential feature, along with senile plaques, of Alzheimer's disease and of senile dementia. However, the neurofibrillary changes in Alzheimer's disease are predominantly cortical (Alzheimer, 1907; McMenemey, 1940), although subcortical nuclei may also be affected (McMenemey, 1958). Muterx (1947) claimed that the neurofibrillary changes occur predominantly in the association areas, and Morel and Wildi (1952) and Schenk (1955) observed that the cortical areas of projection, both afferent and efferent, tend to be spared. These observations vary somewhat from our findings inasmuch as in our cases the changes are equally severe in the hypothalamus and brain-stem as in the cortex. In a patient with manifestations of Creutzfeldt-Jakob disease, Jervis et al. (1942) observed neurofibrillary changes, although as a rule they are not found in other cases of this disease. They have also been reported in subacute inclusion encephalitis by Malamud, Haymaker and Pinkerton (1950), and by Corsellis (1951). Trétiakoff (1919) and Foix and Nicolesco (1925) first described neurofibrillary changes in the pigmented cells of the substantia nigra and the locus caeruleus in cases of Parkinson's disease. Hallervorden (1933, 1935) studied 21 cases of postencephalitic Parkinsonism and observed neurofibrillary changes in the substantia nigra in all cases and in the tegmentum pontis in most of the cases. It was stated that similar changes in the cortical nerve cells were very rare. Neurofibrillary changes occurring in younger patients with postencephalitic Parkinsonism were further noted by von Braunmühl (1949). According to his study, the decreasing order of frequency of neurofibrillary changes is: substantia nigra, locus caeruleus, tegmentum pontis, corpora quadrigemina, hypothalamus, nuclei around the third ventricle, corpus Luysi, red nucleus, pallidum, corpus striatum, dentate nucleus, Ammon's horn, insula, and lastly, the rest of the cortex. Greenfield and Bosanquet (1953) studied 19 cases of idiopathic, 10 cases of postencephalitic, and 5 cases of atypical Parkinsonism, as well as 22 controls. They found neurofibrillary changes in the brain-stem without senile plaques in 9 cases of postencephalitic Parkinsonism and in one with amyotrophy, and in one case of idiopathic Parkinsonism. The authors felt that the neurofibrillary changes differed in some aspects from those found in the cortex and hippocampus in Alzheimer's disease. Greenfield and Bosanquet paid special attention to the midbrain and pons, but examination of the frontal or temporal cortex was not reported. However, they stated as follows: “Even in the case in our series in which paralysis agitans was combined with Alzheimer's disease no neurofibrillary changes were seen in the midbrain or pons, although they have been found there in other cases of Alzheimer's disease.” Later, Beheim-Schwarzbach's (1954) study of “true” paralysis agitans
showed neurofibrillary changes in the substantia nigra in 25 per cent of their cases.

Recently, Tatetsu (1959) reported on a clinico-pathological study of 13 cases of Parkinsonism, 3 of which had had a definite diagnosis of encephalitis in the past. All of his cases showed neurofibrillary changes in the substantia nigra, and 7 out of 13 presented these same changes in the diencephalon and brain-stem. In one of his cases, a patient who died at 29 years of age, psychiatric manifestations in addition to Parkinsonism were present; neurofibrillary changes were distributed widely in the central nervous system.

In spite of the different observations on this subject in the literature, it is interesting to find that neurofibrillary changes often appear in the brain-stem in some forms of Parkinsonism, predominantly postencephalitic, but without senile plaques.

Raskin and Ehrenberg (1956) in their review noted that Alzheimer or Alzheimer-like fibrillary changes have been reported in other conditions such as cholera, dysentery, pellagra, general paresis, and cachexia in man, as well as in various animal experiments.

(4) Intracytoplasmic Granulovacuolar Inclusions

Many of the ganglion cells in our cases contain round or oval granulovacuolar bodies in their cytoplasms. The size of these bodies varies from one to five microns in their greatest diameter. Almost all of them contain a central core which is strongly argentophilic and which stains strongly with haematoxylin. The peripheral zone is unstained, and it appears as a halo. These bodies stand out distinctly and are sharply outlined inside the cytoplasm. A ganglion cell may contain single, few or, occasionally, many of these inclusions. Frequently, the entire cytoplasm is occupied by these bodies, and some of the cells may even lack a nucleus. The granulovacuolar inclusions are noted occasionally in the same areas in which neurofibrillary changes are observed. However, in Sommer's sector they are exceedingly abundant. They appear as a rule in the ganglion cells which fail to show neurofibrillary changes. However, occasionally both changes appear in the same ganglion cells. The clear peripheral zone is not stained with PAS, toluidine blue, thionin, Mallory's phosphotungstic acid haematoxylin, luxol fast blue, Sudan and methylene-blue stains. We feel that these bodies resemble Simchowicz's (1911) "coarsely granular degeneration," and that they are the cells referred to by von Braunmühl (1957) and Greenfield (1958) as "granulovacuolar degeneration."

These bodies, described by Simchowicz (1911), are found to have a similar distribution in our series, in severe cases of senile dementia, in Alzheimer's disease and in some cases of Pick's disease (von Braunmühl, 1957). However, the nature of this form of
degeneration remains unknown. Greenfield (1958) pointed out that "the restriction of granulovacuolar degeneration to forms of senile dementia and almost entirely to one group of cells gives it a special interest." The constant occurrence of these bodies is one of the significant features in our cases. As described above, the pathogenetic relationship between these bodies and neurofibrillary changes is not clearly demonstrated morphologically in our series, although Morel and Wildi (1952) believe granulovacuolar degeneration of nerve cells to be an early stage in the process of "Alzheimerization" on the basis of histochemical studies of their material.

(5) Other Neuronal Alterations

Loss of Nissl substance, chromatolysis, eccentricity of nuclei and other ganglion cell changes are commonly observed. Loss of neurones is always present. In addition, binucleation, neuronalaphagia and satellitosis are not rare. The particular cell swelling and globular argyrophilic inclusions seen in Pick's cortical atrophy are not present in any of our cases. Neither are Lewy's intracytoplasmic concentric hyaline inclusion bodies found in the substantia nigra in any of our cases.

There is no typical senile plaque formation, although occasionally there are a few faintly argyrophilic coagulated structures, resembling early senile plaques. Perivascular plaques of Scholz were not found in any of our cases. The presence of senile plaques is the most constant histological feature in cases of presenile and senile dementia. Generally speaking, senile plaques are a much more common finding in senile cases than are neurofibrillary changes. Only a few exceptional cases are reported in the review by McMenemey (1958) in which there were numerous neurofibrillary changes without senile plaques: Raskin and Ehrenberg (1956) studied 270 cases of patients, ages 60 to 97 years, and found senile plaques in 171 instances, and neurofibrillary changes in 30 cases of which 24 had numerous neurofibrillary changes, and all but one had senile plaques.

There has been much discussion on the histogenesis of senile plaques and Alzheimer's neurofibrillary changes. The mechanisms underlying these changes remain to be clarified.

(6) Loss of Neurones in the Globus Pallidus and Substantia Nigra

Actual loss of ganglion cells is always found in the involved areas associated with severe neurofibrillary changes, granulovacuolar bodies and the other neuronal alterations. However, the globus pallidus and the substantia nigra show more noticeable scarcity of neurones than the other structures in most of the cases in our series. Since the early classical studies by Lewy (1913), Foix and Nicolesco (1925), Bielschowsky (1922), and Hassler (1938), the globus pallidus and the substantia nigra
have been considered to be the site of the most severe ganglion cell damage in Parkinsonism. It is becoming increasingly clear that the substantia nigra is the most consistently involved area in any case of Parkinsonism, whether the idiopathic or postencephalitic form. Other nuclei, such as the locus caeruleus, may also be involved. In this respect, our findings are compatible with those reported in the literature. However, Lewy's concentric hyaline bodies are not present in any of our cases. These inclusions were found in 75 per cent of the cases of Parkinsonism, according to recent investigations by Lipkin (1959). In spite of conflicting reports, as stated previously, there is some indication that Lewy bodies and neurofibrillary lesions are mutually exclusive phenomena, the former being characteristic of the idiopathic and the latter of the postencephalitic type of Parkinsonism. It is of interest that while neurofibrillary changes are common in our cases, they are less numerous in the globus pallidus and caudal portions of the substantia nigra where the severest cell loss and reactive gliosis are most prominent.

(7) Glial Reactions

There is astrocytic gliosis in the involved areas of varying degree, consisting of proliferation of gemistocytic astrocytes and of glial fibres. Microglial reaction is also commonly observed. Subpial and subependymal gliosis is found in varying degrees and is particularly pronounced along the frontal horns and third ventricle. A small number of macrophages containing sudanophilic lipid are found around small vessels, in the cerebral substance and in the brain-stem including the pyramids. There are no inflammatory changes, neither lymphocytes nor plasma cells being found.

(8) Nonspecific Changes Presumably Due to Ageing Process

Accumulation of lipid granules in the ganglion cells is seen in various parts of the cerebral cortex, including Betz cells, basal ganglia, thalamus, inferior olivary nucleus, dentate nucleus, motor nuclei of the brain-stem and spinal cord. The staining characteristics of the lipid granules do not differ from those of ordinary senile cases (Fine et al., 1960). The distribution of this change is identical with that of so-called "lipofuscin." Along with this phenomenon there is some accumulation of iron pigment in the neuroglia and microglia, particularly in the globus pallidus, substantia nigra and in other areas. Certain other changes, such as athero- or arteriolosclerosis and rare minute softenings due to circulatory disturbance, were observed in a few cases.

CLINICO-PATHOLOGICAL CORRELATION

The presence of widespread severe ganglion cell alterations in the cerebral cortex correlates well with the clinical picture of an organic mental syndrome. Severe involvement of the pigmented cells of the sub-
stantia nigra and locus caeruleus in all cases, as well as additional neuronal degeneration of the globus pallidus, are compatible with the Parkinsonian syndrome. The clinical evidence of amyotrophic lateral sclerosis in some of the cases can be correlated with histological changes in the motor neurones, as well as with demyelination of the lateral columns of the spinal cord. Further study is being done on this latter aspect of the disorder.

In general, the pathology of Parkinsonism is not as well defined as the conspicuous clinical features (Heath, 1947; Schwab and England, 1958). It is, however, becoming increasingly evident that the most common lesions are found in the melanin-bearing cells of the substantia nigra and other parts of the brain-stem, in the globus pallidus, substantia innominata and adjacent parts. Of these, the lesion in the substantia nigra has been considered as the most significant pathological finding (Greenfield and Bosanquet, 1953). This is borne out in our series as well. However, Lewy's concentric hyaline inclusions were not observed in any of our cases in contrast to the cases of "idiopathic" Parkinsonism.

The presence of severe astrocytic gliosis and the lack of senile plaques are similar to those in reported cases of Pick's disease. However, the presence of depigmentation of the substantia nigra and lack of distinct lobar atrophy in our series contrast with the gross findings in Pick's disease. Abundant neurofibrillary changes are not a feature of the latter in the majority of cases reported in the literature (Pick, 1892; Malamud and Waggoner, 1943; Hassin and Levitin, 1941; Ferraro and Jervis, 1935).

In regard to the dementia, the presence of abundant neurofibrillary changes and intracytoplasmic granulovacuolar bodies resembles the pathology described in Alzheimer's disease. However, the lack of typical senile plaques and the severe involvement of the substantia nigra and other subcortical nuclei are differentiating features from Alzheimer's disease. For the same reasons, and particularly because of the neurofibrillary changes, our cases also differ from Pick's disease, as stated previously. For although Parkinsonism may on occasion accompany Alzheimer's disease, as in the report of Rothschild and Kasanin (1936) or Pick's disease as in the case described by Akelaitis (1944), our cases differ histologically from the latter.

The clinical symptomatology of dementia with extrapyramidal findings and sometimes with an amyotrophic lateral sclerosis syndrome most closely resembles the Creutzfeldt-Jakob disease. Widespread neuronal damage in our cases may resemble this disorder pathologically, but the presence of the intraganglionic fibrillary changes and the other neuronal alterations again distinguishes them from the original cases described by Jakob (1921), Davison (1932), and others.

It is our opinion, therefore, that in the cases of Parkinsonism on Guam we may be dealing with a different entity than is recognized in either the
presenile dementia or the Parkinsonian syndrome occurring in other parts of the world. It is already noteworthy that all of the 17 cases examined during the past two years on this small island presented common neuropathological features. Moreover, they occurred exclusively among the Chamorro adults.

However, we feel that further study of these and additional cases may give us a key to a better understanding of the presenile and senile neuropsychiatric disorders as well as the Parkinsonian syndrome.

**Summary**

A neuropathological study is reported in 17 cases of a neurological disorder manifested by a Parkinsonian syndrome with mental deterioration found among the natives of Guam. All of the patients were Chamorro adults. The duration of clinical symptoms was about four years and death occurred about the sixth or seventh decade of life. The main macroscopic neuropathological features are the presence of cortical atrophy, and depigmentation of the substantia nigra and locus caeruleus. The consistent finding on microscopic examination is widespread ganglion cell degeneration of the central nervous system. It affects primarily the cortex of the frontal and temporal lobes, Ammon's horn, amygdaloid nucleus, hypothalamus, globus pallidus, thalamus, periaqueductal structures, substantia nigra and tegmentum of the brain-stem. There are numerous intraganglionic fibrillary changes and scattered intracytoplasmic granulovacuolar bodies in the affected neurones of these areas. However, typical senile plaques are not found in any of the cases. In addition, there is a diffuse loss of ganglion cells of variable degree, most marked in the globus pallidus and substantia nigra. Reactive glial proliferation accompanies the neuronal involvement. White matter is relatively well preserved in contrast to a severe involvement of gray matter. Degeneration of motor neurones and bilateral demyelination of the pyramidal tracts are observed in those cases which presented clinically with features of amyotrophic lateral sclerosis. Analysis and discussion of these findings with respect to other forms of dementia and Parkinsonism are presented.

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