GARGOYLISM (HURLER'S DISEASE): A NEUROPATHOLOGICAL REPORT.

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HURLER'S disease is characterized by chondro-dystrophic skeletal changes, corneal opacities, hepatosplenomegaly and mental defect. The skeletal changes are such that the patient presents a large head, grotesque facies, deformed limbs and kyphosis.

Gertrud Hurler (1919) recognized the condition as a clinical entity and described two cases. Henderson (1940) drew attention to the fact that in 1900 John Thompson was first to associate the bizarre combination of clinical signs in one syndrome, but no records were published by him. Berkham (1907) contributed the clinical records of one case, and ten years later Hunter (1917) demonstrated two brothers who are now recognized to have been atypical examples of the disease. Putnam and Pelkam (1925), Helmholz and Harrington (1931) and Ellis, Sheldon and Capon (1936) made notable contributions. The paper by Ellis and his colleagues reviewed the ten cases published up to 1936 and described with a detailed clinical analysis seven other cases which had come under their care.

Pathological studies were initiated by Tuthill (1934) with a description of one of Hurler's cases. This case was complicated by co-existing tuberculous meningitis. Three years later in 1937 Ashby, Stewart and Watkin published a detailed pathological study of one fully investigated case previously presented to the Royal Society of Medicine by Jewesbury and Spence (1921) as a case of acrocephaly with other skeletal deformities.

The neuropathological observations in this case were that ballooned nerve-cells infiltrated with lipid were found throughout the central nervous system, and that these cellular abnormalities were more marked in some situations than in others. In the cerebral cortex deeper lying pyramidal cells were more involved than those near the surface. Profoundly affected nerve-cells were particularly numerous in the optic thalamus, the mid-brain, the dentate nucleus of the cerebellum and the inferior olives of the medulla.

De Lange and others (1936), Kressler and Aegerter (1938) and Kny (1942) made only short reference to their neuropathological findings, but Green (1948) presented the second detailed neurohistological account in the literature of an uncomplicated, fully developed case of Hurler's disease. His case showed a slight disturbance of the characteristic cortical cyto-architectural pattern, a noticeable loss of nerve-cells and an involvement of all cortical neurones by the characteristic pathological process. He mentioned perivascular areas of tissue disintegration in the white matter corresponding to those found by Tuthill. There were compound granular corpuscles in the subcortical white matter. The striatum and pallidum showed severe cell changes, but the thalamus only slight damage. Very little change was detected in the Purkinjë cells of the cerebellum, but the nerve cells of the substantia nigra and the third and twelfth cranial nerve nuclei were in an advanced state of degeneration. The olivary nuclei and the nuclei pontis were well preserved. Although there was moderate gliosis in the cerebral cortex, glial proliferation was inconspicuous in the mid-brain, pons and medulla. The anterior horn-cells of the spinal cord displayed the pathological process most intensely.

Only three* full neuropathological studies of undisputed typical cases are thus available in the literature and of these the two uncomplicated cases fully reported by Green, and by Ashby, Stewart and Watkin show some histological differences. The main characteristic of nerve cell ballooning by infiltration with lipid, however, is well established. A feature which has not received sufficient attention apart from brief mention by Tuthill, is the perivascular lacunation confined to the white matter. This finding represents a conspicuous feature of the morbid anatomy of

* A third case giving a detailed neurohistological account has recently been published by Henderson *et al.* *Arch. Dis. Child.*, **27**, 230, 1952.

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the brain. It is proposed, therefore, to supplement the sparse histological literature on Hurler's disease and to describe and illustrate the lacunar appearance of the white matter.

Case 1 : *M. L—, aged* 9, *male.*

This was a placid, inarticulate idiot of 9. The first available clinical examination showed that the physical signs characteristic of the disease were present at the age of three. The skull was large and frontally bossed. The lower jaw was massive, the teeth spaced out and the nasal bridge depressed. The corneae were larger than usual and showed generalized opacity. Kyphosis was present in the lower thoracic spine, the sternum was sunken and there was a costo-chondral groove. The liver extended to two inches below the rib margins and the spleen was easily palpable. The patient was not deaf.

Death was due to bronchopneumonia.

Pathological Examination.

The brain was not altered in shape. The pia mater presented a ground-glass appearance, and here and there in the parietal region there were small discs of subarachnoid haemorrhage. The basilar artery was exceptionally slender. The gyral pattern was normal, but the sulci were somewhat widened. The whole brain imparted a certain resistance to the feel, resembling poor quality indiarubber, a consistency which was especially appreciable during section. The cut surfaces demonstrated a remarkable condition of the white matter. Arranged radially and in all areas were innumerable oval cystic spaces of varying sizes lying with their long axes in the direction of radiating white fibres. No such spaces were evident in the grey matter.

Nissl preparations showed a mild disturbance of architectural pattern and a slight reduction in cell numbers. Layers III and V were most depleted of cells, whereas the remaining layers were relatively well preserved. The neurones in all cortical areas showed striking changes. The bodies were markedly swollen ; some were only slightly distended, whereas others were extremely dilated and very many had the " ballooned " or " pear-shaped " appearance so characteristically found in amaurotic family idiocy. The Nissl substance had completely disappeared in many and the poorly outlined nucleus could be seen pressed against the cell wall. Where some of the tigroid bodies still remained these were crowded around the periphery of the displaced nucleus, which was very often to be found at the base of the apical dendrite. The nuclei were pyknotic, sometimes staining heavily and sometimes taking little if any stain. The nucleolus appeared in nearly every case deeply stained.

Silver impregnation according to Bielschowsky's method demonstrated a disturbance of the normal fibrillar arrangement. Intracellular neurofibrils were thrust to one or other side against the cell wall, leaving the whole cell occupied apparently by only small shreds of silver-stained material.

All glial cells actively participated in the cortical histological changes. Astrocytes showed proliferative and degenerative changes. Compound granular corpuscles were evident around the small blood-vessels. Oligodendroglial nuclei were pyknotic, but showed no halo formation. Holzer preparations disclosed a severe marginal fibrous gliosis penetrating to the third cortical layer and a milder gliosis extending into the subjacent layers. Proliferated fibrous astrocytes were also apparent in sections stained by the Hortega silver carbonate method. Penfield's stain confirmed diffuse microglial proliferation and an increase in the numbers of oligodendroglia.

The neuronal and perivascular fat was demonstrable by a number of lipid staining methods. Herxheimer's Scarlet Red, Sudan Black, Kay and Whitehead's Sudan IV, Jackson's Acetic-carbol-Sudan III and Telford Govan's modification of Sudan III staining in aqueous media were employed.

Herxheimer's method revealed the presence of crowded globules of fat in the ballooned neurone. In the severely affected cell the lipid seemed to displace all other intracellular elements to one side, and in other cases where the deposits were smaller they appeared to originate at a point directly opposite the main axonal base. Sudan III stained the lipid inclusions deep orange and Sudan Black stained them black.

The strikingly prominent feature of the white matter was the oval radiating " cysts." These were not devoid of structure, and in Perdrau stained preparations a fine reticulum was easily visible. In van Gieson stained sections the strands appeared to be fibroblastic and of adventitial origin arising from the vessel invariably situated within the space. Fibroblast nuclei were visible, and numerous large fat engorged compound granular corpuscles could be seen. In the subcortical white matter where the smaller oval spaces were generally situated the cysts were often crowded with these cells. They were less obtrusive in the large cysts in the deeper reaches of the white matter. The cyst wall showed evidence of demyelination, and Holzer preparations demonstrated a dense ring of fibrous gliosis along the cyst margin. Herxheimer's Scarlet Red stained the fat contained in the gitter cells within the spaces a brilliant red, whereas the intraneuronal inclusions stained orange.

The remaining white matter showed generalized moderate fibrous gliosis throughout, and severe gliosis in some regions.

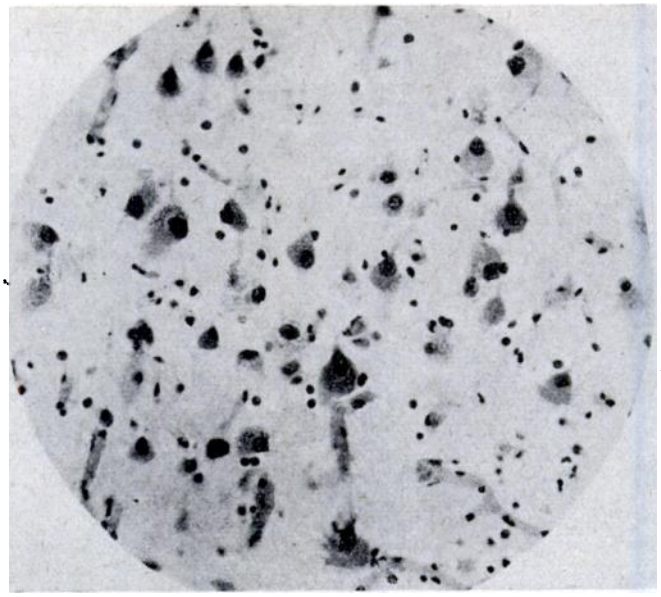

FIG. 1.—(Case 1). *Parietal cortex.* × 240. Nissl. The nerve-cells show the typical vacuolation of the cytoplasm and ballooning of the cells seen in lipid infiltration.

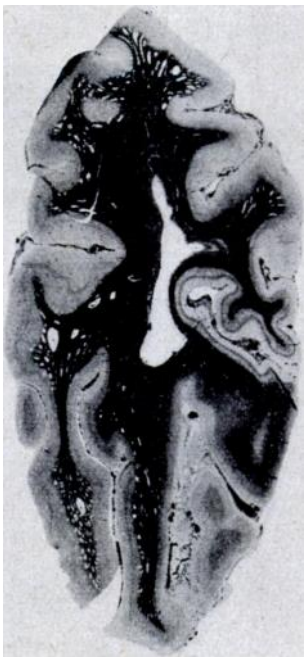

FIG. 2.—(Case 1.) *Occipital lobe.* × 1·5. Heidenhain. Numerous oval lacunae are found in the white matter and are generally radially arranged.

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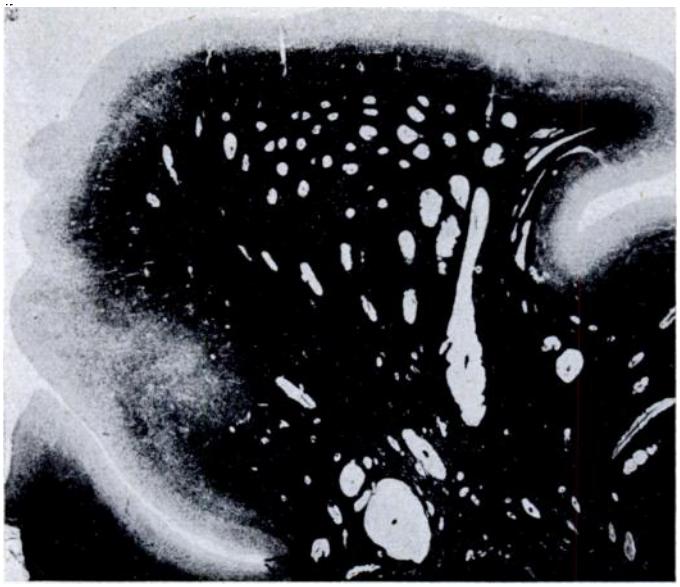

FIG 3.—(Case 1.) *Occipital lobe.* × 6. Heidenhain. The lacunae are oval and often elongated. There is almost invariably a vessel within each space.

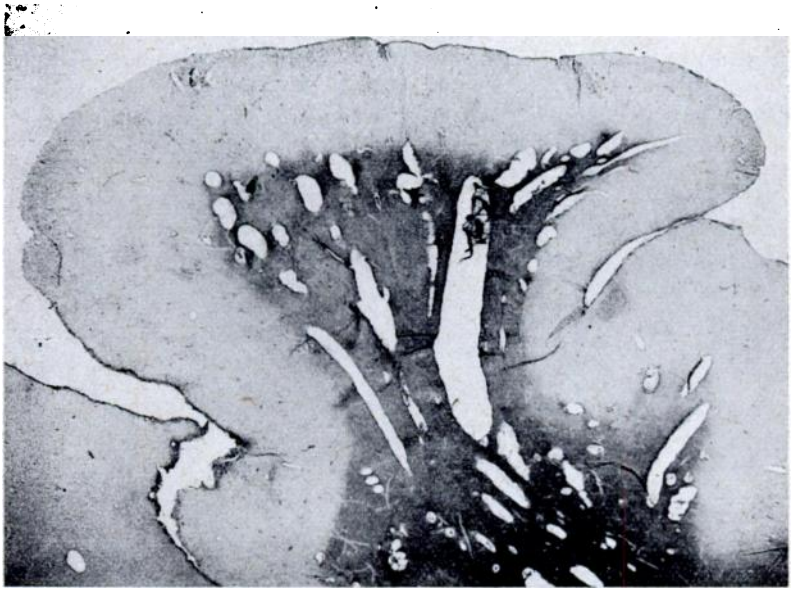

FIG. 4.—(Case 1.) *Occipital lobe.* × 6. Holzer. The white matter shows generalized severe fibrous gliosis. The lacunae are bounded by a thin dense band of gliosis.

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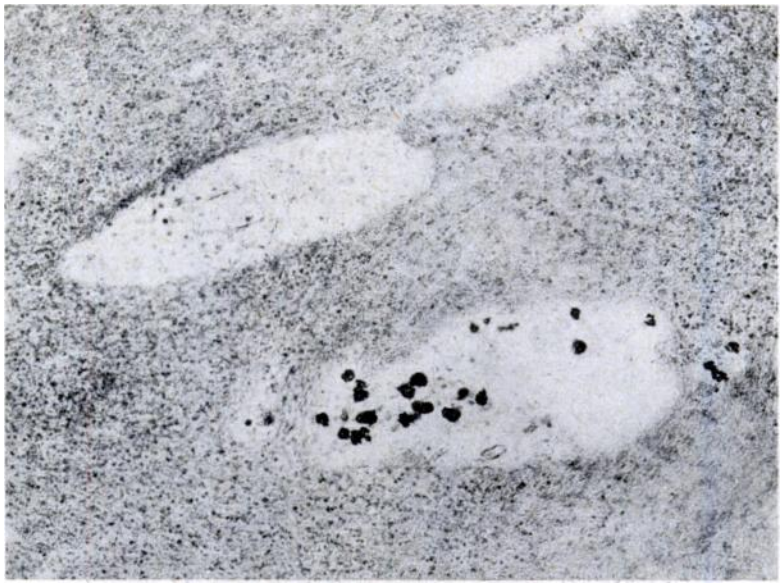

FIG. 5.—(Case 1.) *The lacunae.* × 120. Herxheimer. Compound granular corpusles within the lacunae.

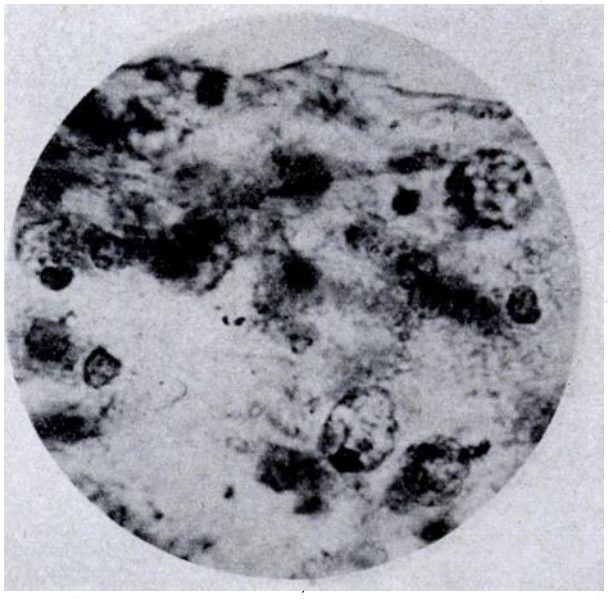

FIG. 6.—(Case 1.) *A lacunar wall.* × 810. Herxheimer. Compound granular corpuscles in the lacunar wall.

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The typical cell changes in the caudate nucleus were as common as the cell changes of the cortex. The large cells were more severely affected than the smaller ones and this incidence upon the large cell was also seen in the putamen. There was a concomitant increase in all glial elements. The pallidal cells showed involvement, and many of them had almost totally disappeared, leaving only a faint outline. The neurones of the thalamus were nearly all involved, but not to the same degree as the large cells of the corpus striatum. Notwithstanding the apparent ubiquitous involvement there were groups of normal cells.

Herxheimer's fat method demonstrated a great deal of lipid in the cells of the basal ganglia. but the smaller neurones appear to contain only a small volume of intracellular fat. Hortega and Holzer preparations disclosed a considerable gliosis.

Brain stem ganglion cells, particularly in the cranial nerve nuclei, were as involved as the neurones of the cortex, but the cells of the pontine nuclei appeared not very heavily damaged. The cells of the inferior olivary nuclei were in a good state of preservation. The hypoglossal nucleus was the site of most intense damage. There was extensive gliosis in the brain stem, but most marked was the subependymal fibrous gliosis in the floor of the fourth ventricle. Heavily gliosed also was the dorsal nucleus of the vagus nerve.

The molecular layer of the cerebellum was normal and the granular layer showed no atrophy. The Purkinjë cells stained very lightly and were slightly reduced in numbers. Many of the remaining cells were moderately affected. The dentate nucleus did not show much ballooning of its cells. Numerous small perivascular cysts were visible in the cerebellar white matter and each was delimited by a thin band of gliosis. The cerebellar white matter, however, was not so densely gliosed as the cerebral white matter.

In the spinal cord all neurones presented some degree of ballooning and a few reached very large proportions. The myeloarchitecture of the cord was undisturbed and there was comparatively little gliosis.

Case 2: *W. W—, aged* 5, *male.*

This was a placid, inaccessible, inarticulate low-grade imbecile.

The first full examination at the age of four showed a large skull, massive mandible, sunken nasal bridge, opaque corneae, spaced-out teeth, kyphosis of the lower thoracic spine and a mongoloid " trident " hand. The protuberant abdomen showed an umbilical hernia. The liver and spleen were both enlarged.

Death was due to bronchopneumonia.

Pathological Examination.

The cerebral and cerebellar hemispheres were symmetrical. The meninges showed increased vascularity and small areas of thickening and opacity of the pia arachnoid. The membranes stripped easily, revealing a normal convolutional pattern without atrophy. The vessels were normal.

Nissl preparations showed considerable cortical architectural disturbance in some areas and very slight alteration in others. The distribution of light and heavy damage did not follow any regional plan. In the most affected foci there was a disorientation of all layers with considerable numerical reduction in nerve cells. In the least affected areas the architecture was normal but abnormal individual cells were demonstrable.

These abnormal neurones showed ballooning, disappearance of Nissl substance, displacement of the nucleus to one side, and distension of the cell body with fatty inclusions. Bielschowsky preparations showed neurofibrillar displacement in the most affected cells. The occipital cortex showed the greatest incidence of damage. In this region there were certain areas where no normal cell was seen, and some nerve-cells showed very severe swelling and gross distortion of their contours. The parietal and temporal lobes were affected next in order of severity. The Ammon's horn showed involvement of the neurones of the endfolium, but there appeared to be no reduction in cell numbers. The dentate fascia was not affected.

There was a great proliferation of glial cells in all areas, particularly in and around foci of maximal cell loss. Astrocytes showed both proliferative and degenerative forms. There was a marked increase of microglia. Oligodendroglial nuclei showed pyknosis. Holzer sections demonstrated a narrow band of dense marginal gliosis not extending further than the molecular layer except in areas where the cell loss was great. Microglial cell proliferation was evident, particularly in Penfield preparations.

Herxheimer's scarlet red stained the intracellular fat a deep orange. Sudan black stained the inclusions black and Sudan III by various techniques a pale orange.

The cerebral white matter in all sections demonstrated innumerable oval spaces arranged with their long axes radially placed. Microscopic examination showed that each of these cysts contained a vessel situated centrally and running along the greatest diameter, and that each space, although apparently empty macroscopically, was actually made up of a fine reticular network enmeshing many gitter cells. The reticulum itself showed fibroblastic nuclei. Each cystic space was bounded by a moderately dense area of fibrous gliosis, and within this area and for a short distance around there was demyelination. The corpus callosum contained a large elongated cyst about a centimetre in length. The reticu-

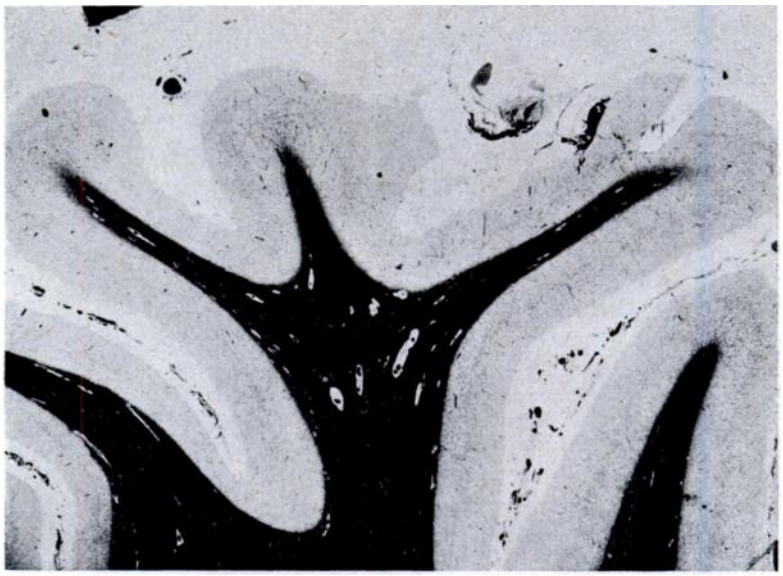

FIG. 7.—(Case 2.) *Occipital lobe.* × 5·5. Heidenhain. Numerous radially arranged lacunae are seen.

FIG. 8.—(Case 2.) *Corpus callosum.* × 5·5. Heidenhain. A large single lacuna situated centrally in the corpus callosum.

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lation within this space was coarse, and the individual strands were thick, showing fewer nuclei, but the interstices of the formation contained fat-laden gitter cells. This space, like the others, was bounded by dense gliosis.

The striatum was severely affected. The large cells were maximally involved, and a major proportion of the small cells was also damaged. The large cells of the globus pallidus had almost all disappeared; only a few ghost cells remained. The nerve-cells of the thalamus and of the hypothalamic nuclei were involved, but nowhere in these regions was the severe change common in the cortex to be seen.

All glial elements showed considerable proliferation spread throughout the whole extent of the basal ganglia. Gliosis was most dense in the subependymal regions.

The nuclei of the cranial nerves, particularly the hypoglossal, were most extensively damaged, and resembled the most damaged areas found in the cerebral cortex. The nigral

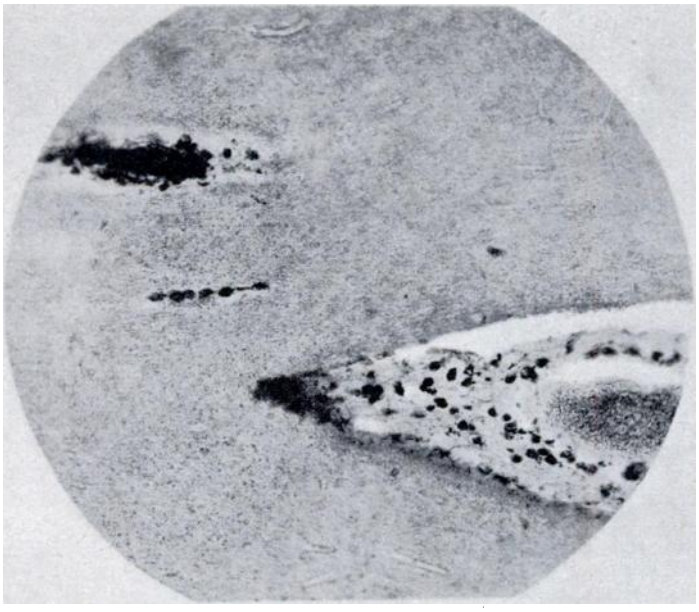

FIG. 9.—(Case 2.) *Lacunae.* × 100. Herxheimer. The lacunae contain numerous fat-laden scavenger cells and a reticulum surrounding a central vessel.

cells showed changes similar to those in the cranial nuclei and there was considerable extracellular pigment. The pontine nuclei, however, showed little pathological change, and the inferior olives demonstrated no lesion.

There was moderate glial proliferation in the brain stem. Heavy gliosis was present in the subependymal area in the floor of the fourth ventricle.

The molecular and granular layers of the cerebellum were intact, but the usually lipophobic Purkinjë cells were affected. The degree of damage of these cells did not vary greatly and no examples of severe distortion were evident. The cells of the dentate nucleus were moderately affected. The cerebellar white matter showed numerous small cystic spaces, as did the cerebral white matter. Specially stained sections disclosed a reticulum, enmeshed compound granular corpuscles, and a band of surrounding fibrous gliosis. There was demyelination for a small area around each cyst.

In the anterior horn of the spinal cord were typical damaged cells. Many of these cells were in the process of disintegration. The spinal cord was only mildly affected by gliosis, and there was no evidence of tract demyelination. In Herxheimer stained sections the lipid inclusions stained deep orange. Other fat stains were employed, but no atypical staining reactions were evident.

Special examination of material taken from both cases by the use of various lipid solvents did not give any clear evidence as to the nature of the lipid material.

Discussion.

Hurler's disease falls into that now large category of lipid disturbances which includes Tay-Sachs' disease, Nieman-Pick's disease, Gaucher's disease and Hand-Schuller-Christian disease. Hurler herself emphasized only the skeletal manifestations of the syndrome when she called her first cases dysostosis multiplex, and Washington (1939) introduced the term " lipochondrodystrophy " in an attempt to include under one title all the pathological findings. The term " gargoylism " also stresses the unfortunate facies and skeletal changes of these patients.

The neurohistological similarities and differences shown by the cases of Tuthill, of Ashby, Stewart and Watkin, and of Green, and the two here presented warrant some analysis. The individual nerve-cells show identical changes in all five cases, and there is a remarkable similarity in the distribution of the most severe lesions. The cortex in all except Tuthill's case shows pronounced involvement, but on the whole no one layer or one type of cell suffers more damage than others. The large cells of the striatum are severely affected in four out of five cases. The thalamus is severely damaged only in Ashby, Stewart and Watkin's case, and the pallidum is degenerated markedly only in the second case presented in this communication. The hypoglossal suffers maximally among the cranial nerve nuclei. The substantia nigra is moderately severely involved, whereas the pontine nuclei are remarkably well preserved.

The cerebral and cerebellar white matter are described in Tuthill's case as having widely distended spaces surrounding the vessels. She believed these to be the end result of adventitial hypertrophy. The two cases presented in this contribution show this change in a very striking way. The perivascular lacunation was entirely confined to the white matter, no " cyst " being detectable in the cortex. The smallest vessels in the white matter, however, were often free from perivascular distension; the larger vessels invariably showed the spaces. It is possible that these spaces may be due to the distensile effect of an undue overcrowding of lipid substance around the vessels in the process of scavenging. The presence of a fine reticulum within the spaces and the failure to demonstrate the cysts around the smaller vessels where gitter cells were occasionally to be seen suggests that mechanical distension cannot wholly account for the finding. The dense mural fibrous gliosis and the circumjacent loss of myelin can be explained by the prolonged course of this disease. These two observations were conspicuous in the larger cysts, which showed little crowding with gitter cells, and were therefore presumably older. The loss of myelin is likely to be a direct consequence of the cyst formation and local nutritional failure.

Solubility tests by immersion of formalin fixed frozen sections in various lipid solvents followed by staining with lipophilic dyes seem not likely to add any substantial information to the study of this disease. Diagnosis of the precise chemical nature of the deposits from their staining properties with Sudan III has, as yet, no sure foundation. The nature of the lipid can only be elucidated by adequate biochemical work. Lindsay and his colleagues (1948) have suggested that a macromolecular substance allied to glycogen is involved and Smith and co-workers (1952) have produced evidence to show that the disease does not chiefly involve lipids. In a recent contribution Brante (1951) states that " Gargoylism should perhaps be conceived as a general disturbance in the metabolism of either the aminohexoses, the polysaccharides or the lipopolysaccharides." He also states that the subject of a subsequent paper will be a case showing a great increase of a polysaccharide-sulphuric acid ester in many tissues including the liver.

Summary.

The neuropathology of two typical cases of Hurler's disease is presented. The ubiquitous alteration of nerve-cells by ballooning due to infiltration and distension by a lipid is described confirming the main finding in the previous reports on this subject.

The special feature described and illustrated in this communication is a widespread perivascular lacunation and vascular adventitial hypertrophy found throughout the white matter.

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