A CASE OF JUVENILE AMAUROTIC FAMILY IDIOCY

BY

R. M. NORMAN, STOKE PARK COLONY

INTRODUCTION

SINCE the original description in 1903 by Batten¹ of a juvenile type of amaurotic family idiocy the main clinical and pathological features of this variant of the condition have become well established. Recently, Sjögren² has shown in an analysis of 59 affected families that its inheritance is determined by a single recessive Mendelian factor. The various types of amaurotic idiocy named clinically according to time of onset as infantile, late infantile, juvenile and adult, differ essentially in the composition of the lipoids which are characteristically present in the neurones. The diminishing severity and more protracted course of the symptoms manifested in the older patients are matched pathologically by a gradation in the composition of the lipoids ranging from the prelipoids of the infantile forms to the complex substances closely resembling normal lipochrome found in the juvenile and adult cases. The importance of these lipid changes has been accentuated in recent years by the discovery of the occasional association of infantile amaurotic idiocy with a widespread lipid histiocytosis (Niemann-Pick's splenohepatomegaly) and it is still a matter of controversy whether the main ætiological factor in amaurotic family idiocy rests on a primary disorder of lipid metabolism rather than on a primary neuronal degenerative process. Before such problems can be elucidated it is evident that more observations will have to be made, and since the following case presents many interesting features I have thought it worthy of record.

For permission to publish these clinical and pathological notes I am indebted to Professor R. J. A. Berry, the Director of Medical Services at Stoke Park Colony.

CLINICAL ASPECT

The patient, a female, age 14 years and two months, was admitted to Stoke Park Colony in April 1930. The records state that she was an illegitimate child of a woman reported as being of poor mentality. The mother subsequently married and by the second union has had seven unaffected children. The patient made little progress at school, although actually reaching Standard IVb. On admission to the Colony she was more or less helpless, having to be dressed and washed. On examination she was found to be partially blind in both eyes, light perception only being present. Both optic discs were atrophic, with very small arteries. There was slight peripheral pigmentary change. No macular pigmentation was present. There was an error of refraction of + 3.5 in both eyes. The Wassermann reaction of the blood was negative. Apart

from loss of power, examination of the nervous system showed no striking abnormality. Speech, however, was monotonous and indistinct and there was occasional incontinence of urine. Her mental age was estimated at about six years by a modified Binet-Terman test. Physical measurements at this time showed an all-round reduction from normality. Thus the cubic capacity of skull as calculated from Lee's formula No. 14 was 1,251 c.c., which is normal for a child of 10 years of age. Standing and sitting stature was retarded by two and three years respectively. Right and left grips were extremely poor (12 kilos and 8 kilos) as was her vital capacity of 1,100 c.cm. Her weight of 39.6 kilos, however, was within the range of normal variability for her age.

Towards the end of 1930 the patient developed epileptic fits, and for the next two years her history was one of slowly progressing physical and mental deterioration. The blindness never became absolute. Little change was observed in the periodicity of the epileptiform convulsions, which appeared in short bouts once or twice a month. In September 1933, being unable to get about even with assistance, she was admitted to the chronic ward of the Colony Hospital. Here she led a vegetative existence for the remaining seven months of her life, almost blind, speechless, but occasionally noisy, generally immobile and apathetic, but retaining a voracious appetite to the end. Bronchitis and hypostatic congestion of the bases of the lungs soon appeared, the latter condition being the precipitating factor in her terminal illness. Death occurred on April 18, 1934, at the age of 18 years and three months. The skull was injected with formol saline solution through the orbits immediately after death, and an autopsy was made about four hours after death.

MORBID ANATOMY

1. *Macroscopic Appearances.*—Both bases of the *lungs* were deeply congested but not consolidated. A remarkable degree of adiposity was displayed in many parts of the body.

The *heart*, which was small, showed extensive fat-deposition in the subepicardial region. The cardiac muscle was pale and abnormally friable. Fatty deposits were present beneath the endocardium, especially over the mm. papillares and upon the tricuspid valve.

The *liver* also showed fatty changes. It was slightly enlarged with somewhat rounded edges. The cut surface was pale in colour with a faint yellowish tinge. The *spleen* was normal in size, very dark and friable. The *kidneys* appeared normal. The *uterus* was infantile.

An accumulation of fat was found under the epicranial aponeurosis. There was a general excess of fat throughout the peritoneal cavity. The *thyroid gland* was very small.

The *calvaria* was thick and the diploë almost absent in places. The *dura* was adherent to the skull over the posterior part of the superior sagittal sinus. The brain and cervical spinal cord were removed, and after blocks had been taken for fixation in ammonium formol bromide were suspended in formol saline. The whole brain seemed firmer to the touch than is usual for fresh specimens. The cerebral convolutions showed a slight degree of atrophy which was most marked in the frontal lobes. The sulci in this region showed abnormal widening in both hemispheres.

On the *right side* the central sulcus was bifid at both extremities, neither

of the upper prolongations reaching the mesial surface of the hemisphere. The fissuring of the external part of the parietal and occipital lobes was most irregular (fig. 1). A short intraparietal sulcus $\frac{3}{4}$ inch in length (a) ended a transverse sulcus (b) which apparently represented the transverse occipital sulcus although lying anterior to the parietooccipital fissure (c). The latter was continued over the external surface of the hemisphere and intersected the upturning end of the superior temporal sulcus (d). This abnormal

FIG. 1

transverse continuation of the parietooccipital fissure was joined above by a prolongation of the intraparietal sulcus (e), and below by the upper extremity of a well-marked lunate sulcus. The frontal lobe was microgyric and its frontal operculum very poorly developed, a small part of the insula being visible. Its V-shaped lower boundary was separated from the Sylvian fissure by a sulcus $\frac{1}{2}$ inch long.

On the *left side* also the occipital lobe was most unusually convoluted. The parietooccipital fissure divided into two terminal branches on the mesial surface of the hemisphere. The lower of these appeared in the normal

manner for a short distance upon the convexity. Between these two terminal branches, however, a deep sulcus took origin and pursued a curved course on the external surface of the occipital lobe, finally dividing itself into two parts—one part passing downwards in lunate formation to the occipital pole, the other passing upwards and nearly reaching the upturned end of the superior temporal sulcus. The superior temporal sulcus, instead of ending in an angular gyrus, passed inwards to terminate in the lower part of the intraparietal sulcus. The intraparietal sulcus, as on the right side, ended in a transverse occipital sulcus which lay level with the upper branch of the parietooccipital fissure. Other abnormalities present were a poorly developed superior temporal gyrus and a small frontal operculum bounded—as on the right side—by a Y-shaped sulcus.

2. *Microscopic Appearances of Nervous System.*—Frozen sections were prepared from nine different areas of the left cerebral cortex, from thalamus and subthalamic area, midbrain, pons, upper and lower medulla and cervical spinal cord. The cerebellar cortex was also examined. The following staining methods have been employed :—

- (1) For Nissl's bodies—toluidin blue.
- (2) For neurofibrils—Bielschowsky's method.
- (3) For astrocytes—Cajal's gold sublimate, Hortega's silver carbonate and Holzer's method.
- (4) For microglia—Hortega's method and modifications.
- (5) For myelin—Anderson's modified Kulschitsky-Pal method.
- (6) For lipoids—Scharlach R, Nile blue, osmic acid and the method of progressive mordanting.

(a) *Changes in the Neurones.*—Low-power views of the various regions examined showed that little apparent cell destruction had taken place. The cortical areas presented the familiar cytoarchitectural peculiarities usually associated with imbecility, viz. a poorly developed third layer of pyramidal cells and poverty of granular cells. While it is true that the general arrangement of cells was somewhat distorted by the characteristic swelling of the larger neurones, the impression given was that of a badly developed cortex and not a normal one in a degenerate condition (fig. 2A).

Under higher magnification the typical neuronal changes found in juvenile amaurotic idiocy were observed, namely, pear-shaped swelling of the cytoplasm due to the lipid aggregations pushing the healthy part of the cytoplasm, nucleus and neurofibrillæ to a peripheral part of the cell (see fig. 2B, 2C, and 2F. These changes were found with great uniformity in all the regions examined, the ganglion cells of the thalamus being the most obviously affected. In the cervical spinal cord one could distinguish an occasional large ventral horn cell in which the changes were minimal. In the cerebral cortex there seemed to be little evidence of any sites of predilection on the part of the disease-process. The majority of the Betz-cells showed little swelling, the lipid aggregations being small and closely

FIG. 2

resembling the lipochrome deposits in senile brains. In the occipital lobe the stria of Gennari was well preserved, and in general this region presented none of the disorganization which characterizes the late infantile form of amaurotic idiocy. In Bielschowsky preparations the affected portion of the cytoplasm usually stained as a granular detritus (fig. 2G, and fig. 4B). Occasionally, however, as in the thalamus (fig. 2E), a reticulated appearance was given. No swelling of the axons was observed outside the cerebellum.

In the *cerebellum* the folia of the superior surface showed little reduction in the numbers of Purkinje cells, though here and there cells were represented as mere shadows. Most of the cell-bodies and many of the dendrons (fig. 3A), were distended. In the more atrophic folia of the lower surface, especially near the vermis, far fewer Purkinje cells were in evidence. Axonal ballooning was occasionally observed (fig. 2D). The granular layer was well preserved. In Bielschowsky preparations the neurofibrillæ appeared in the form of a thick bundle pushed to one side of the distended cell-body (fig. 2C). Only rarely could the basket fibres be demonstrated around the less affected cells.

(b) *The Nature of the Lipoid Content.*—In the cerebral cortex and cerebellum the lipoid was usually present in a uniformly staining mass, while in the thalamus and substantia nigra it had a granular distribution (fig. 2F). The latter appearance was associated in Bielschowsky preparations with a reticulated formation in the cytoplasm. In the subcortical white matter small aggregations staining an intense red with Scharlach R were occasionally seen. In unstained sections the lipoid deposit of the larger neurones showed as faint yellow. Toluidin blue stained it a greenish-blue colour, Scharlach R a yellowish-orange (in the thalamus a distinctly redder shade) and Nile blue a deep blue colour. Negative results were obtained with osmic acid after 24 hours' chromication and with the progressive mordanting method using Anderson's modification of the Kulschitsky-Pal stain and examining sections daily up to seven days' mordanting. The lipoid was extremely resistant to solvents and could be demonstrated after 24 hours' immersion in acetone, ether and chloroform and even after rapid treatment with hot xylol.

(c) *Changes in the Neuroglia.*—In the cerebral cortex slight degrees of subpial gliosis were commonly present, especially in the more atrophic frontal convolutions, where long strands of hypertrophic glial fibres were present in the superficial layer (fig. 3D). Regressive rather than proliferative changes, however, were more in evidence. In sections stained by Cajal's gold sublimate method a condition closely resembling that found in senile brains was observed, viz. an increase in the size of the cell-body, delicate vascular feet and wavy processes (fig. 3C). Silver impregnation methods gave a somewhat different picture, a different sort of cell being brought into prominence. In these sections the nucleus of the cell was often pyknotic and the processes took the form of club-shaped expansions (fig. 3F). Another type of glial cell was often found liberally distributed in the superficial parts of the molecular layer of the cerebral cortex (fig. 3E). Here so-called amœboid

FIG. 3

changes were present, consisting of a retraction of the processes and great increase in the size of the cell-body. Again there is a resemblance to a senile state. Lipoid stains were taken up very feebly or not at all by these glial cells. In the thalamus, however, granules staining red with Scharlach R were present around the glial nuclei.

In the thalamus and molecular layer of the cerebellum (fig. 3B) there was considerable overgrowth of glial fibres in the form of long leashes or bundles. A tendency to subpial fringing in the latter organ could often be made out in Holzer preparations.

(d) *Microglia and 'Mulberry' Cells*.—Microglia cells of elongated bipolar form were present in the cerebral cortex. These rod-cells showed varying degrees of swelling and retraction of their processes (fig. 4D, 4E and 4F), and in some areas, especially the occipital, seemed to be represented as the plume-like formations illustrated in fig. 4A.

The so-called mulberry cells which have been described in cases of juvenile amaurotic idiocy were frequently seen in sections stained by Hortega's method for microglia. They were most common in the frontal association area, and all types of transitional forms were present from single cells simulating compound granular corpuscles (fig. 4c) to the lobulated formations which have given rise to the designation 'mulberry' (fig. 4B). This resemblance to microglia cells has been noted by Globus,³ who explains their vacuolated appearance as due to the disappearance of their original content after treatment with fat-dissolving reagents. In my sections they did not stain with Scharlach R with the intense red colour of compound granular corpuscles, so whatever their content may be, it is not a prelipoid.

(e) *Myelin Sheaths*.—There was a poverty of super- and inter-radial fibres in the cerebral cortex, but the picture did not differ from that usually found in imbecile brains. No tract degeneration was found in the cervical spinal cord.

DISCUSSION

In discussing recorded cases of juvenile amaurotic idiocy Greenfield and Holmes⁴ suggested that two main types could be distinguished—those in which the cerebellum was particularly involved and those in which the cerebellum and rest of the nervous system were equally affected. Their own case belonged to the former group and exhibited gross general atrophy, much gliosis and great reduction in the cells of the granular layer. In this classification it would appear that the case described in this paper falls into the second group, for the cerebellum was normal in size and its granular layer well preserved. It may well be that the typical ballooning of dendrons and axons shown by the Purkinje cells, which was not found in other parts of the nervous system, is due to an inherent susceptibility on the part of these cells to react in this manner, for similar changes are encountered in senile dementia and other diseases.

The lipoid content of the cells closely resembles in staining reactions

FIG. 4

that found by Hurst,⁵ who examined in detail Greenfield and Holmes's material. It differs mainly in the fact that Hurst was able to demonstrate poorly stained granules after four days' mordanting by the Kulschitsky-Pal method. He formed the opinion that the lipid present was a mixture of phosphatides and cerebrosides. The lipid granules in the thalamus of my case stained a deeper red than the more diffuse orange-red deposits in the cortical neurones, though they showed no other difference in solubility or staining reaction. This intenser red colour of the thalamic cells is usual, according to Hassin,⁶ in the late infantile or Bielschowsky-Jansky type of amaurotic idiocy. Such minor variations in the lipid as are shown in this case are to be expected, for—as Bielschowsky⁷ has pointed out—the precise composition of the lipid seems to vary in each affected family.

Another feature worthy of emphasis was the state of adiposity found at the autopsy. This was all the more remarkable in a clinical condition often associated with ultimate marasmus. In the introduction to this paper I have noted that theories of the pathogenesis of amaurotic family idiocy have recently been modified owing to the discovery of Niemann-Pick's spleno-hepatomegaly, a condition in which the infantile form of amaurotic idiocy is associated with a widespread lipid histiocytosis. The view now held by Bielschowsky, Sachs and others is that the pathological changes both in the nervous system and elsewhere are due to a primary disturbance of lipid metabolism. The present case of juvenile amaurotic idiocy is, therefore, of peculiar interest, for it presents evidence of lipid abnormalities outside the nervous system. On the other hand, the clearly abnormal fissuring of the cerebral cortex, especially in the parietooccipital region, is entirely in keeping with the conception of a hereditarily determined cortical agenesis. Such unmistakable evidence of irregular prenatal cortical growth is the usual finding in the imbecile and idiot brains of primary aments.⁸ It would appear that a compromise is necessary between the two extremes of opinion on the point whether the causative factor in amaurotic idiocy is primarily neuronie or lipoidal in character. The following quotation from Globus sums up the position excellently :—

'It is now commonly accepted that no sharp line can be drawn between the chemical composition of the cell and its morphology ; one is dependent on the other. It is also agreed that regressive morphological alterations may be provoked by an inadequate provision of constructive cell material essential for normal cell growth. Thus is it not probable that cells poorly endowed with constructive material may, at some critical moment in their life, when exposed to some unfavourable condition, be arrested in the process of growth ? With their development so interrupted and brought to a stop, it is quite conceivable that regressive changes may set in and these may show apparent similarities to alterations revealed in processes of degeneration.'

EXPLANATION OF FIGURES

- Fig. 1. The external surface of the right occipital lobe.
- Fig. 2. (a) Frontal association area (F.D.). Toluidin blue. $\times 48$.
 (b) Superior parietal lobule (P.E.). L III. Toluidin blue. $\times 360$.
 (c) Cerebellum. Two Purkinje cells. Bielschowsky's stain. $\times 450$.
 (d) Cerebellum. Swelling of axon of Purkinje cell. Bielschowsky's stain. $\times 270$.
 (e) Thalamus. Bielschowsky's stain. $\times 450$.
 (f) Thalamus. Scharlach R and haematoxylin. $\times 360$.
 (g) Precentral gyrus (F.A.). A medium pyramidal cell. Bielschowsky's stain. $\times 600$.
- Fig. 3. (a) Cerebellum. Swelling of dendrons. Bielschowsky's stain. $\times 450$.
 (b) Cerebellum. Overgrowth of glial fibres in the molecular layer. Hortega's silver carbonate method. $\times 270$.
 (c) Superior parietal lobule (P.E.). Infragranular cortex. Astrocytes of senile type. Cajal's gold sublimate method. $\times 270$.
 (d) Area peristriata (O.A.). L I. Overgrowth of glial fibres. Hortega's silver carbonate method. $\times 450$.
 (e) Frontal association area (F.D.). L I. 'Amœboid' glia. Hortega's method for microglia. $\times 1,000$.
 (f) Precentral gyrus (F.A.). Regressive changes in the astrocytes. Hortega's method for microglia. $\times 600$.
- Fig. 4. (a) Area peristriata (O.A.). L III. Microglia in the form of deeply impregnated rod-cells. Hortega's method for microglia. $\times 270$.
 (b) Frontal association area (F.D.). 'Mulberry' glia. Hortega's method for microglia. $\times 360$.
 (c) As in (b). Glial cells simulating compound granular corpuscles. $\times 270$.
 (d) Rod-cells from parietal cortex. Cone and Penfield's modification of Hortega's microglia method. $\times 800$.
 (e) As in (d), showing slight retraction and swelling of the processes. $\times 1,000$.
 (f) Rod-cell from precentral gyrus (F.A.), showing more advanced swelling of the processes. Hortega's method. $\times 1,000$.
 (g) Frontal association area (F.D.). Bielschowsky's stain. $\times 270$.

REFERENCES

- ¹ BATTEN, F. E., *Trans. Ophthalmol. Soc.*, 1903, **23**, 390.
- ² SJÖGREN, T., *Hereditas*, 1930, **14**.
- ³ GLOBUS, J. H., Penfield's *Cytology and Cellular Pathology of the Nervous System*, 1932, **3**, 1177.
- ⁴ GREENFIELD, J. G., and HOLMES, GORDON, *Brain*, 1925, **48**, 183.
- ⁵ HURST, E. W., *Brain*, 1925, **48**, 1.
- ⁶ HASSIN, G. B., *Histopathology of the Peripheral and Central Nervous System*, 1933, 316.
- ⁷ BIELSCHOWSKY, M., Penfield's *Cytology and Cellular Pathology of the Nervous System*, 1932, **1**, 178.
- ⁸ BERRY, R. J. A., and NORMAN, R. M., *Jour. Neurol. and Psychopath.*, 1934, **14**, 289.