The lipidoses and the central nervous system. By Alan Bird. From the Department of Pathology, The National Hospital, Queen Square, London. Brain 1948; 71: 434–450

Once the retinal features of amaurotic familial idiocy had been recognized by Waren Tay ([1843–1927]: Symmetrical changes in the region of the yellow spot in each eye of an infant. Transactions of the Ophthalmological Society of the United Kingdom 1881; 1: 55–57) and with the subsequent elucidation of nerve cell changes in this and related disorders by (Bernard) Sachs ([1858–1944]: On arrested cerebral development with special reference to cortical pathology. Journal of Nervous Mental Disease 1887; 14: 541–54), the concept of diseases in which lipid accumulates in cells of the reticulo-endothelial system and in neurons gained momentum. Now, Dr Alan Bird wishes to report three cases of Tay–Sachs disease and one of the disorder in neurons described by (Philippe) Gaucher ([1854–1918]: De l’épithélioma primitif de la rate, hypertrophie idiopathique de la rate sans leucémie [academic thesis]. Paris, 1882) and suggest, tentatively, a classification for the neuronal lipidoses.

Several forms of amaurotic familial idiocy are already described: congenital cases in which death occurs soon after birth; an infantile form ‘with a marked predilection for Jews and affecting[ing] females three times as frequently as males’ in which development is arrested at the age of 6–8 months with subsequent mental deterioration, weakness, blindness due to retinal ganglion cell degeneration with the appearance of a cherry-red spot, noise-evoked myoclonus, inability to swallow and death within a year from onset; a broadly similar late-infantile form, delayed in onset, often without the cherry-red spot, showing no racial selection and following a more prolonged course; slowly progressive juvenile amaurotic familial idiocy manifesting as intellectual deterioration, spasticity, blindness due to involvement of the outer granular layer and retinitis pigmentosa, and cerebellar involvement; and an adult form that combines extrapyramidal symptoms and signs, incoordination, bulbar involvement and retinitis pigmentosa with optic atrophy. Of course, not every case fits this classification; nor is the inverse relationship between age at onset and presence of the cherry-red spot invariably seen.

The disease described by (Albert) Niemann ([1880–1921]: Ein unbekanntes Krankheitsbild. Jahrbuch für Kinderheilkunde. Neue Folge (Berlin) 1914; 79: 1–10) and (Ludwig) Pick ([1868–1935]: Der Morbus Gaucher und die ihm ähnlichen Krankheiten (die lipoidzellige Splenohapatomegalie Typus Niemann und die diabeteische Lipoidzellenhypoplasie der Milz). Ergebnisse der Inneren Medizin und Kinderheilkunde (Berlin) 1926; 29: 519–627)—also preferentially affecting female Jewish infants—selectively involves the liver, spleen and lymph nodes and spares the nervous system. But several authors, including (Ludo) van Boegaert (1897–1989), have reported families in which Tay–Sachs and Niemann–Pick disease co-segregate. This also resembles the story of evolving knowledge on Gaucher’s disease: ‘for long it was believed that the changes [are] confined to the reticular cells of the lymphohaematopoetic organs…however…up to 1946…25 cases of Gaucher’s disease involving the central nervous system [are described]. The clinical picture is characteristic: ‘an infant with hepatosplenomegaly of early onset, perhaps with pigmented skin and pingueculae, regresses mentally into a state of apathy and somnolence with catatonia. Marked muscular hypertonia produces increased reflexes, opisthotonus with neck rigidity…strabismus…trismus, dysphagia and…laryngeal spasm…marked cachexia…usually caus[ing] death within a year’.

Many consider that nervous system involvement is confined to the infantile form of Gaucher’s disease; but, anticipating his own case, Dr Bird cites examples already in the literature of neurological conditions in adults that have the histological features of Gaucher’s disease although not diagnosed as such even following neuropathological examination: ‘symptoms and signs formerly regarded as pathognomonic of one group are known to appear sporadically in an apparently distant group, thus pointing to some underlying factor common to all forms. This factor is the infiltration of nerve cells with lipid; it is present in every type as is borne out by the literature and the cases now to be described’.

The patient Alan Bird describes with Gaucher’s disease, admitted to Chase Farm Hospital in Enfield (UK) in 1942 under the care of Dr Russell Brain (1895–1966), is unusual in that presentation was at school age and both the reticulo-endothelial system and central nervous system are involved. From the age of 7 years, V.C. (now aged 11) exhibits behavioural disturbances and mental deterioration being facile, unable to converse or recognize his family, incontinent and with petit mal seizures. General examination shows splenomegaly and lymphadenopathy. He dies 6 months after undergoing elective splenectomy. At autopsy, the neurons, especially of the third and fifth layers of the motor cortex are swollen and ballooned with displaced nuclei (Fig. 1): ‘a few of the dendrites had globular swellings, some immediately adjacent to the...
nerve cell...isolated dendrites showed “staghorn” broadening reminiscent of the condition described as occurring in the cerebellum typically in the juvenile form of amaurotic idiocy'. Similar changes are seen in the thalamus, caudate nucleus, putamen and globus pallidus, the mid-brain, medulla and anterior horn cells of the spinal cord. The normal arrangement of Purkinje and basket cells in the cerebellum is disrupted (Fig. 2). All affected neurons have intracellular granular swellings. Their nature cannot be identified using any conventional stains but: ‘these staining reactions are in accord with descriptions of those of the lipid in the spleen in Gaucher’s disease’. Turning to that organ, the reticular cells are diffusely hypertrophied, multinucleated and with fine granular cytoplasm that does not stain with Sudan III, the Schlarlach or Smith–Dietrich methods, or after boiling. These are typical Gaucher foamy cells, in places broken down and phagocytosed by histiocytes (Fig. 3); and they are also present in the liver and lymph nodes. Biochemical investigation carried out some years after the tissue was fixed in formalin shows a considerable increase in cerebrosides in both the brain and spleen.

‘The chief interest of this case lay first in the age of the patient, most cases of Gaucher’s disease with nervous system involvement...having been infants...and...in the striking similarity in the histopathological changes between it and cases of amaurotic family idiocy’.

Aged 3 years, A.H., the only child and female of non-Jewish parents is admitted to the National Hospital (London, UK) under the care of Dr M.J. Mc Ardle (1909–89) with incoordination, dysarthria and seizures that are difficult to control, followed by generalized myoclonus and progressive blindness. She dies 19 months after presentation. At autopsy, carried out by Dr J.G. (Godwin) Greenfield (1884–1958), nerve cells of the cerebral cortex—and of the thalamus, putamen and globus pallidus, brainstem, spinal cord and cerebellum (which has lost its usual arrangement of Purkinje and basket cells)—are distended with fine granules of lipid that stain an orange-red colour with Schlarlach R and haemalum exactly similar to that described in amaurotic familial idiocy by Greenfield and (Sir Gordon) Holmes [(1876–1965): The histology of juvenile amaurotic idiocy. Brain 1925; 48: 183–217]. Many cells are undergoing degeneration with evidence for neuronophagy; and some have burst discharging their lipid content. Throughout, there is an intense glial reaction. Both eyes are removed and, in addition to altered retinal ganglion cells in keeping with the appearance of neurons, the outer nuclear layer has disappeared and the macula is a dark red spot surrounded by a zone of pigmentation. The lipid material is soluble only in chloroform and identified as one of the sphingomyelins.

A second case, P.L., the child of non-Jewish first cousins, starts to show behavioural and mental deterioration aged 5 years, with seizures, unsteadiness and loss of vision. She deteriorates and progresses steadily, dying at the age of 9 years. At autopsy, carried out by Dr Greenfield, the reticulo-endothelial system is normal but the central nervous system shows lipid infiltration of nerve cells with degeneration and reduction in their number, and reactive change in glia mainly affecting the motor cortex but with involvement of the basal ganglia, brainstem, spinal cord and cerebellum. The retina shows complete loss of rods and cones from the outer granular layer at the macula and extending to the periphery of the retina (Fig. 4). The pigmented changes are less marked than in the previous case. Few details are available on Dr Bird’s fourth case in whom development was delayed as an infant with death aged 18 months from pneumonia. Neurons throughout the cerebral cortex, basal ganglia, medulla and spinal cord contain lipid and stain with Scharlach; the cerebellar architecture is not disrupted.

The work of others has identified the lipid that accumulates in Gaucher’s disease as glucocerebroside; as sphingomyelin in Niemann–Pick disease; and as sphingomyelin and a phosphatide-free carbohydrate-containing lipid ganglioside in amaurotic familial idiocy. ‘These substances are closely related to one another as both cerebrosides and sphingomyelins arise from the same precursor, lignoceryl-sphingosine.’ Present normally, lipid causes harm in excess through mechanical rather than biochemical effects. ‘It is believed that there is an imbalance of the enzymes concerned with lipid anabolism and catabolism within the cell leading to an accumulation of lipid’ forcing aside the nucleus of the neuron, its axon and dendrites and causing chromatolytic changes. At first, function is maintained but the accumulation of material displaces the neurofibrils and eventually the neuron bursts. Although demyelination may occur in patches of the white matter, these changes are regarded as subsidiary to those in grey matter: but ‘the apparent tendency in certain age groups for one part of the brain to be

Figure 1 Cerebral cortex, showing varying degrees of lipid accumulation in the neurons, some being almost normal, others very degenerated. Thionin stain for Nissl granules. (From Bird, 1948).
affected more than another may be related to the process of myelination... myelin, once laid, is not stored statically but is in a state of chemical equilibrium, molecules being constantly added to and removed from the complex’. However, commentators have not seen anything in the comparative histology from different types of case to deviate from the consensus that each represents a variant of the same disease entity. Despite some differences with respect to involvement of the cerebellum and variations in staining with the Scharlach reagent, the four cases confirm this view not only with respect to the infantile and juvenile forms of amaurotic familial idiocy but also the single example of Gaucher’s disease. It is because the link between these cases is the lipid infiltration and associated degeneration of nerve cells, that Dr Bird proposes to introduce the term ‘neuronal lipidosis’ to embrace all members of these closely related groups, and to settle difficulties such as the anomalous situation of ‘amaurotic familial idiocy sine amaurosis’. Moreover, his classification is in line with current trends in the nomenclature of neurological disease to group rather than...
separate closely related entities. Dr Bird’s tentative proposal for the neuronal lipidoses is:

(a) cerebroside neuronal lipidoses associated with cerebroside infiltration of reticular-endothelial cells (Gaucher’s disease); and
(b) phosphate neuronal lipidoses: (i) without involvement of reticulo-endothelial system (amaurotic family idiocy etc.); (ii) with involvement of reticular-endothelial system (Niemann–Pick disease).

The subsequent history of the lipidoses is one of significant therapeutic success. In 1981, Sheridan Snyder and Henry Blair started a company (Genzyme Corporation) devoted to finding drugs that would cure ‘orphan’ conditions resulting from deficiency of enzymes essential for human survival even though these affect only a small number of individuals. Material extracted from 20,000 human placentas was required to manufacture enough Alglucerase, a modified form of human β-glucocerebrosidase in which the non-reducing ends of the oligosaccharide chains are terminated with mannose residues, to treat each patient with type 1 Gaucher’s disease for one year. The Food and Drugs Administration approved Ceredase® (the trade name for Alglucerase), given as intravenous therapy, in 1991 and around 1000 patients eventually received the treatment. This was largely replaced by Cerezyme® (Imiglucerase: a recombinant DNA-technology produced analogue of human β-glucocerebrosidase) at a nominal cost of at least $200,000.
annually per patient for life, although financial dispensations are provided for many of the 6000 individuals treated worldwide. Life expectancy for individuals with Gaucher’s disease confined to the reticulo-endothelial system is now normal but, disappointingly, there is less to be gained for the 10% of treated patients in whom the central nervous system is also affected. Alan Bird concludes that neurons engorged with lipid simply burst and are destroyed by mechanical forces, eliciting a surrounding glial response. He does not focus on the cellular components of that glial response but as with many forms of neurodegenerative disease, the contribution of inflammation is considered part of the primary disease process or at least a significant amplifier and mediator of tissue injury. Now, a cytotoxic role for activated microglia in the neuronopathic forms of Gaucher’s disease, triggered once a critical level of glucosylceramide storage is exceeded, leading to the release of inflammatory cytokines that amplify the inflammatory response and adding to the neuronal loss, is proposed as the main mechanism of tissue injury (see Vitner et al., page 1724).

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