Archives of Disease in Childhood, 1987, **62**, 1056–1059

Historical article

Tay-Sachs disease: a centenary

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VOL. XIV. September and October, 1887. Nos. 9 and 10.

THE

Journal

OF

Nervous and Mental Disease.

Original Articles.

ON ARRESTED CEREBRAL DEVELOPMENT, WITH SPECIAL REFERENCE TO ITS CORTICAL PATHOLOGY.[1]

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NEW YORK.

OUR knowledge of the pathological substratum of the various forms of mental derangement is still very imperfect. In the majority of cases, there may be no marked changes in the structure of the brain; or, if

One hundred years ago Sachs[1] published in great detail the clinical features, diagnostic signs, and pathology of a patient with a 'new' condition which, with that of Warren Tay,[2] was to bear his name. Sachs did not know in 1887 that Tay had forestalled him.

In 1881 Tay (1843–1927) described the case of a 12 month old infant who from the age of 2 or 3 weeks had increasing weakness of the neck and limbs. Of the optic fundi he wrote; 'in the region of the yellow spot in each eye there was a conspicuous tolerably defined large white patch, more or less circular in outline, and showing at its centre a brownish red, fairly circular spot . . . which seemed to be a gap in the white patch through which one saw healthy structure.' This is well shown in the colour plate accompanying the case report. Tay called in his two colleagues Jonathan Hutchinson (1828–1913) of the eponymous teeth and Hughlings Jackson (1835–1911) of epilepsy fame. The great neurologist could throw no further light on the case, saying there seemed no evidence of cerebral affection to account for the weakness. Six months later at post mortem examination the sole cerebral abnormality noticed was a large cavity containing old blood clot outside the left lateral ventricle.[2]

Warren Tay, a general surgeon, ophthalmologist, and dermatologist, was 'an untiring hospital officer . . . adding the subject of pediatrics at the Hospital for Children Hackney Road. . . . He was a walking dictionary at the London Hospital in the nineties,'[3] and 'would suffer even fools gladly.'[4]

Bernard Sachs (1858–1944) was a different sort of man, outgoing, humorous, and widely known. He was president of the New York Academy of Medicine and in 1931 president of the First International Congress of Neurology in Berne. He wrote nearly 200 papers and a text book. His parents were said to have eloped from Bavaria to Baltimore where Bernard was born. Although he maintained his German contacts, he was American in mind and preferred to be called Barney.[5]

After four years at Harvard he entered the medical school at Strasbourg, a recent German conquest, at a time when the Johns Hopkins, Cornell, and New York medical schools did not exist. He went on to study under Charcot in Paris, eventually becoming professor of neurology at the New York Polyclinic and attending physician at Mount Sinai, Montefiore, and Bellevue Hospitals.

In July 1887 he presented his paper on 'arrested cerebral development' before the American Neurological Association. It was published in October the same year and described the progressive condition from the age of 2 to 3 months, until death at the age of 2 years, of a girl whose mother had been thrown out of a carriage when five months pregnant. The child's progressive weakness gave normal muscular response to galvanic and faradic stimulation. The decreasing intellectual process was accompanied by loss of vision, but not of hearing. As Sachs wrote, 'The slightest touch and every sound were apt to startle the child.'

Neither Tay nor Sachs coined the famous phrase 'cherry red spot', but Sachs quoted the report of the New York and Berlin ophthalmologist Herman Joseph Knapp (1831–1911): 'Child two to three months; nystagmus vibratorius . . . Fovea centralis of a cherry red colour surrounded by an intense greyish white opacity.' Knapp is said to have reported his findings at the 17th meeting of the Heidelberg Ophthalmological Society, as published in the proceedings of that meeting, but I have been unable to trace this.

When Knapp saw the child again at 1 year and ten months she was totally blind with complete optic atrophy: 'disc as white as paper with scarcely any trace of blood vessels. Maculea lutea essentially as before'. (It is doubtful if neurologists used ophthalmoscopes at that time. The electric ophthalmoscope was invented later by Charles Henry May (1861–1943) of New York.) The patient's eyes were not examined after death, but the optic nerves were variously stained and found to be normal. 'Blindness must therefore have been due either to the retinal changes or to the deficient cortical condition, or to both'.[1] Sachs noted that similar fundal appearances had been reported by Magnus and by Goldzieher, but without explanation. According to Sachs, their reports appeared in 1855.

Sachs's own account is distinguished by careful pathology with detailed descriptions of convolutions and sulci, and there is a striking photograph of the brain after fixation. Blocks were made from six sites on each cerebral cortex, and sections cut from all except the cuneus which was too brittle, although paraffin and celloidin embedding were already in use at that time.[6] Pronounced changes in shape, axis, nuclei and nucleoli were found in the small and large pyramidal cells, with hardly any of a normal appearance. 'In some cells a partly normal and partly pathological character of the cell body is visible'. Neuroglia and white matter were normal. There are two drawings (×70 and ×500) by Ira Thompson van Gieson (1866–1913) whose name survives today in the connective tissue stain, and whose initials IvG may be seen on each plate. In the same year 1887 Wadsworth[7] of Boston described a further case, acknowledging the priority of Sachs's paper. Sachs's colleague, the ophthalmologist Knapp, contributed to the ensuing discussion.

Later developments

Three years after his first communication Tay reported that three children in the original family had by then been affected.[8] Four years later he noted consanguinity of the parents in another case.[9] In 1888 Kingdon[6] mentioned Jewish parentage, but Sachs[10] accumulated further information: as a Jewish physician working among the large Jewish population in New York, by 1896 he had encountered 19 cases. The disease was 'almost exclusively observed in Hebrews', and he commented on how often parents were related by blood.

There the matter rested for nearly half a century until the galactolipid (GM_2 ganglioside) stored in the brain was identified.[11–15] Enzymologists discovered the enzyme which was missing in affected children,[16–17] and showed reduced concentrations in their parents.[18] The condition was thus defined as a lipid storage disease due in the infantile form (type 1) to deficiency of hexosaminidase A, with high concentrations of hexosaminidase B. The way was then open to radical prevention. Partial enzyme deficiency can be detected in carriers of the gene and affected fetuses during pregnancy.

Tay and Sachs

The two discoverers looked at their observations rather differently. Warren Tay was interested in identifying the disease and its nature, and left a particularly good record of the appearance of the optic fundi. Bernard Sachs in his first report was concerned not so much with the particular disease as with the relationship between mind and brain.[1]

'Our knowledge of the pathological substratum of the various forms of mental derangement is still very imperfect. In the majority of cases, there may be no marked changes in the structure of the brain; or, if there be any changes at all, they are entirely beyond our ken, and cannot be made out by our present methods of investigation. As mental pathology is in its infancy it is but natural that we should first seek for structural changes in those conditions in which the departure from the normal is greatest, in which the mind is disturbed as a whole, and not merely with reference to a single part or faculty; though I shall at once declare my belief that derangement of a part of the mind means disorganisation, more or less complete, of the entire mental mechanism.

While we are even now in possession of many facts concerning the morbid structural changes in dementia paralytica, changes that accompany the complete dissolution of a fully developed and once normal mind, we have busied ourselves but little with the morbid changes that often affect the brain, and consequently the mind also, when both are yet undergoing the process of evolution. These cases of retarded development, of idiocy, of mental imbecility, call them what you will, seem to me to possess a deep pathological and physiological interest. From the pathological changes found in these cases of extreme mental defects, we are entitled to draw an inference regarding the normal functions of those nervous elements here found deficient, and we may well argue with regard to such broad facts as an absolute lack of mentality, although it may be a long time to come before we shall be able to explain the morbid mechanism underlying fixed delusions, hallucinations, and the like, or to state exactly what the structural changes are in paranoia, in circular insanity, and in other grave mental troubles. The condition which I have the privilege of discussing before you to-day represents not only such changes as come about in the process of evolution, but represents changes of the earliest period of infantile development.'

I thank Dr Rosemary Stephens for advice and the librarians of the Royal Society of Medicine for assistance.

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References

1 Sachs B. On arrested cerebral development, with special reference to its cortical pathology. *J Nerv Ment Dis* 1887;**14:** 541–3.
2 Tay W. Symmetrical changes in the region of the yellow spot in each eye of an infant. *Trans Ophthalmol Soc UK* 1881;**1:**55–7.
3 Anonymous. Obituary of Warren Tay. *Lancet* 1927;**i:**1161.
4 Anonymous. Obituary of Warren Tay. *Br Med J* 1927;**i:**487.
5 Kennedy F. In memoriam—Bernard Sachs 1858–1944. *Am J Psychiatr* 1943–44;**100:**853–4.
6 Kingdon CC. A rare fatal disease of infancy, with symmetrical changes at the macula lutea. *Trans Ophthalmol Soc UK* 1888;**12:**126–37.
7 Wadsworth OF. A case of congenital, zonular, greyish-white opacity around the fovea. *Trans Am Ophthalmol Soc* 1886–1887;**4:**572–3.
8 Tay W. A third instance in the same family of symmetrical changes in the region of the yellow spot in each eye of an infant, closely resembling those of embolism. *Trans Ophthalmol Soc UK* 1884;**4:**158–9.
9 Tay W. A fourth instance of changes in the yellow spot region of an infant, closely resembling those in embolism. *Trans Ophthalmol Soc UK* 1888;**12:**125–6.
10 Sachs B. A family form of idiocy, generally fatal, associated with blindness (amaurotic family idiocy). *J Nerv Ment Dis* 1896;**21:**475–8.
11 Klenk E. Beitrage zur der lipidosen (3 Mitteilung). *Hoppe-Seyler's Zeitschrift für Chemie* 1939–1940;**262:**128–43.
12 Klenk E. Uber einem weiteren Fall von infantilen amaurotischer Idiotie (Typ Tay-Sachs), *Hoppe-Seyler's Zeitschrift für Chemie* 1941;**267:**128–44.

[13] Klenk E. Neuraminsäure, des Spaltprodukt eines neuen Gehirnlipoiden. *Hoppe-Seyler's Zeitschrift für Chemie* 1941;**268**:50–8.
[14] Klenk E. Über die Ganglioside, eine neue Gruppe von zuckerhaltigen Gehirnlipoiden. *Hoppe-Seyler's Zeitschrift für Chemie* 1942;**273**:76–86.
[15] Svennerholm L. The chemical structure of normal human brain and Tay-Sachs ganglioside. *Biochim Biophys Res Commun* 1962;**9**:436–41.
[16] Robinson D, Sterling JL. N-acetyl-beta glucosaminidase in human spleen. *Biochem J* 1968;**107**:321–7.
[17] Okada S, O'Brien JS. Tay-Sachs Disease: generalised absence of a beta-D-N-acetyl hexosaminidase element. *Science* 1969;**165**:698–700.
[18] O'Brien JS, Okada S, Chen A, Fillerup DL. Tay-Sachs disease detection of heterozygotes and homozygotes by serum hexosaminidase assay. *N Engl J Med* 1970;**283**:15–20.

Forty years ago

Icterus neonatorum: its incidence and cause

L Findlay, G Higgins, and M W Stanier (Oxford)—Arch Dis Child 1947;**22**:65–74

In this paper Findlay and his colleagues set out to determine the incidence and cause of "physiological jaundice". With a definition of hyperbilirubinaemia as a plasma bilirubin >1 mg/dl (17·1 μmol/l), the incidence was 81% in 73 infants. No correlation was found between the concentration of bilirubin in umbilical cord blood and the maturity of the fetus, but premature infants were more likely to develop jaundice than mature ones. Only four of the 73 infants, however, were below 35 weeks' gestation. A current theory that icterus neonatorum was due to excess haemolysis was dismissed on the basis of haematological studies, such as the haemoglobin curve during the first three months, and the absence of appreciable erythroblastosis or of reticulocytosis after the first few hours of life. On the other hand, the search for evidence of the failure of the neonatal liver to excrete bilirubin at the normal adult rate had to depend on tests that, by the standards of today, were inadequate for the purpose—for example, analysis of plasma proteins, the Takata-Ara reaction, and measurement of faecal bilirubin excretion. Not surprisingly, most test results were inconclusive, but the authors, having excluded excess haemolysis on reasonably satisfactory evidence and having found some diminution in the excretion of bilirubin by the infant with jaundice compared with the infant without jaundice in the first few days of life, concluded that icterus neonatorum was due to hepatic immaturity.

Comment. It may be difficult for younger paediatricians to realise that in 1947 little or nothing was known of the conjugation of bilirubin in the liver cells, of the binding of bilirubin to albumin in the plasma and extracellular fluid, or of the enterohepatic circulation.
(Leonard Findlay was one of the few British paediatricians with a truly international reputation before the second world war. In 1923 his appointment as Professor of Medical Paediatrics in the University of Glasgow was the start of the first University Department of Paediatrics in any British University. He built a great reputation for his studies on rickets, rheumatic fever, and congenital syphilis. He was among the first to integrate clinical paediatrics with the basic sciences. Findlay was an autocrat with argumentative tendencies. In 1930 in his early 50s he quarrelled with his colleagues in Glasgow and moved to the Princess Elizabeth of York Hospital in London. In London, and later in Oxford, he never seemed to make the impact on international paediatrics that had characterised his work in Glasgow. He died while the above paper was 'in press'.)

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