

AMAUROTIC IDIOCY *

GENERAL AND HISTORICAL CONSIDERATIONS WITH REPORT OF A CASE

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Amaurotic familial idiocy—a clinical entity of which about one hundred cases are on record, is of great interest to the general medical profession because its symptoms are relatively so definite but rarely so correlated by the observer as to be recognized as the disease we are about to discuss.

The forerunners of the discovery of this disease were the ophthalmologists, chief of whom was Warren Tay,¹ who, in 1881, published an article under the caption “Symmetrical Changes in the Region of the Yellow Spot in Each Eye of an Infant.” Tay found that in his patient, a child of 12 months, in the region of the macula, there was a large whitish patch, in the center of which was a brownish red spot similar to that caused by embolism of the central artery of the retina. He considered this change probably a local congenital disturbance. Later, in 1884, he reported² three more cases with the same condition in the same family, all of whom died at 2 years of age.

Three years later B. Sachs³ made his noteworthy observations on the character of this disease in a paper on “Arrested Cerebral Development.” In 1892 he reported a second case in the same family. Both children died at 2 years, had the same clinical symptoms and signs, and the brain of each showed the same pathologic changes. Sachs could give no explanation of the causes of this disease but said they were probably fetal-genetic.

Carter⁴ first recognized that the cases thus far corresponding to Sachs' were of Hebraic extraction and that “while to date, the majority of the cases reported belong to that race, by no means do all.”

The term “amaurotic family idiocy” was proposed by Sachs in 1896, when the familial character of this disease was almost uniformly found. To this time 19 cases were described as having occurred in ten families. Combining the symptoms of all the cases

* Submitted for publication March 24, 1915.

1. Tay, Warren: Tr. Ophth. Soc. United Kingdom, 1881, i, 55.

2. Tay, Warren: Tr. Ophth. Soc. United Kingdom, 1884, iv.

3. Sachs, B.: Jour. Nerv. and Ment. Dis., 1887, xiv, 541.

4. Carter: Knapp's Arch. Ophth. and Otol., 1894, xxiii, 126.

then known Sachs was able to arrive at a definite symptom-complex which he says is pathognomonic:

1. Mental impairment in first few months of life leading to absolute idiocy.
2. Paresis or paralysis of the greater part of the body—flaccid or spastic in type.
3. Reflexes may be deficient or increased.
4. A diminution of the vision, terminating in absolute blindness (changes in the macula lutea and later an optic-nerve atrophy).
5. Marasmus and a fatal termination as a rule about the second year.
6. The occurrence of the affection in several members of the same family.
7. Healthy at birth, remaining so up to the third or fifth month; and occasionally —
8. Nystagmus.
9. Strabismus.
10. Hyperacuity of hearing.
11. Inordinate laughter was present in one case, and
12. Disturbances in deglutition were occasionally observed in others.

This syndrome then, as described by Sachs, is one made up of a number of symptoms most of which occur in many other organic nervous diseases, but chief stress up to this time was placed on its familial character, racial predisposition and the fact that it occurred shortly after birth.

It remained for Vogt⁵ in 1905 to describe a condition in young children similar to that which Sachs described in infants. This author considered these juvenile cases a separate entity and he proposed the term "juvenile family amaurotic idiocy" for them. The findings in his patients were that the disease is familial in character, has no predilection to the Jewish race, begins in early youth, leads slowly to blindness, frequently to paralysis, and death occurs after several years.

Vogt had six cases (two in one family, one in the second and three in the third) in all of which the children were normal to the fourth to seventh year when there was gradual onset of blindness with optic-nerve atrophy (one case showed frequent deposits in the retina), dementia, paralysis and death from two to fifteen months later.

Vogt states that he believes Tay-Sachs' disease and the juvenile form of family amaurotic idiocy represent different degrees of the same process, but that Tay-Sachs' disease is so sharply characteristic that it may well retain its name.

Soon after this Batten⁶ described two more cases of the juvenile type, one patient having "fits," together with dementia and retinal changes. His patients, like most of those cited above, died of marasmus.

5. Vogt: *Monatschr. f. Psych. u. Neur.*, 1903, xviii, 163, 320.

6. Batten: *Tr. Ophth. Soc. United Kingdom*, 1903, xxiii, 386.

Mayon,⁷ Higier,⁸ Ichikawa,⁹ Wandless,¹⁰ Dercum,¹¹ Turner,¹² Gordon¹³ and others have added materially to this list so that now there are probably about thirty cases of the juvenile type on record.

In a paper of this character a paraphrase of each case would be out of place, but a combination symptom-complex of the reported cases shows normal growth and development until 3 years or later, failing mentality and sight (with gradual optic-nerve atrophy and retinal changes), gradual onset of paralysis (flaccid or spastic), with or without convulsions; irritability of temperament, nystagmus, familial tendency without predilection to the Jewish race; death usually from marasmus.



Fig. 1.—Patient D. F., aged 7 months.

The following clinical and pathologic report of the author's case may serve further to emphasize the close relationship between the two types of amaurotic idiocy.

D. F., a girl, aged 6, entered the Children's Hospital because of "fits." Neither her parents nor any of her antecedents were of Hebraic extraction. Both parents are living and well and are not related. The daughter of a maternal uncle "had no control of her body at birth and died of brain trouble at between 4 and 6 months." A maternal granduncle died of "brain fever" at 14 years. There is no specific history in either parent. The Wassermann test in the mother's serum was negative. She had one miscarriage but no stillbirths. The patient was born at full term after a two-days' labor terminating with a hard, high forceps delivery. The child was fed with proprietary foods from the first and never nursed. Its mother claims that the infant was kept

7. Mayon: *Tr. Ophth. Soc. United Kingdom*, 1904, xxiv, 142.

8. Higier: *Deutsch. Ztschr. f. Nervenheilk*, ix, 1.

9. Ichikawa: *Klin. Monatsbl. f. Augenheilk.*, 1909, xlvii, 73, 432.

10. Wandless: *New York Med. Jour.*, 1909, lxxxix, 953.

11. Dercum: *Jour. Nerv. and Ment. Dis.*, 1897, xxiv, 396.

12. Turner: *Brit. Jour. Child. Dis.*, 1912, ix, 193.

13. Gordon: *New York Med. Jour.*, 1907, lxxxv.

drunk with gin for the first month of life. She was a fat but not strong child. A severe attack of pertussis occurred in the second year, but subsided without complications. This was soon followed by "inflammation of the bowels" with high temperature, but recovery was complete.

From 2 to 2½ years the patient ran, played and talked — an active, healthy, apparently normal child. (See Figs. 1, 2 and 3.)

At 3 she had "black measles." This was followed by "food poisoning" after eating canned deviled ham. The patient nearly succumbed. About three months later she had an attack of "indigestion" accompanied by unconsciousness and stiffness of the whole body. Recovery ensued which was followed by the measles.

Just about this time (age 3½ years) the mother noticed that the child had a slight limp. A chiropractic physician was called who found the hip was "out" about one-half inch. This he replaced without benefit to the child.

The patient's eyes began to "wander with a bewildered look" and a few days later she awakened with "attacks of crying and trembling and rigidity of the arms and legs which lasted for a few minutes." These attacks increased in frequency, as many as twenty a day being noted. Sometimes one side alone, sometimes both sides, and at others the head or arms alone were convulsed.

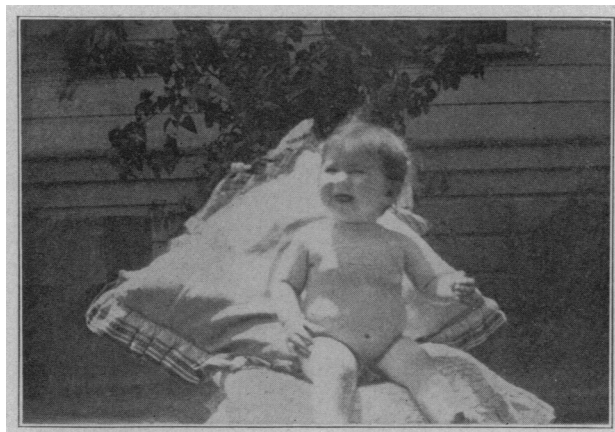


Fig. 2.—Patient D. F., aged 9 months.

After some of these attacks the patient showed strabismus the rest of the day. A sudden noise or jar would bring on a "spasm."

Because of increasing rigidity, which became rather constant about six months after onset, the patient was unable to help or feed herself and could not walk. From a bright, healthy, active child within six to eight months she became a dull, apathetic, inactive invalid who gradually ceased to notice objects about her. (See Fig. 4.) The bowels were obstipated, necessitating daily enemas. Urination was involuntary.

Three years after the onset of the disease the patient presented the following positive findings:

A poorly nourished girl, only the purely vegetative functions persisted. Uncovering the patient or even clapping the hands in the vicinity of the bed, slamming the doors, etc., caused marked convulsive movements of the extremities and opisthotonus which lasted from ten to fifteen seconds.

There was a striking growth of hair on the extensor surfaces of the arms, legs and labia majora and the upper part of the back. The average length of these hairs measured three-fourths of an inch. The hair generally was thick and moist.

No scars or eruptions were present but the skin of the neck was deeply pigmented.

No cranial deformities were present.

Eyes: The child was blind. No spontaneous nystagmus or ocular palsies were noted. The left pupil was larger than the right; both reacted very sluggishly to light and measured from 4 to 5 mm.; bilateral optic atrophy was present and the retinal vessels were very narrow. In the region of each macula there was a grayish-white area in which was seen a small brownish-red spot. The retina, besides being very thin, showed no deposits or abnormal changes elsewhere. This finding was confirmed later by Dr. L. D. Green.

Ears: These showed marked hyperacuity of hearing. No visible pathologic changes were noted.

Mouth: The upper incisors were separated 3 mm. No anomalies of dentition were present. The palate was high arched. Frequent gnashing of teeth (trismus) occurred during examination.

Glands: The thyroid and thymus were small; the pectoral and posterior cervicals shotty, the inguinals large.

Chest: The lungs and heart were negative. The abdomen also was negative.



Fig. 3.—Patient D. F., aged 13 months.

Spine: With the patient in the sitting position the head fell forward, backward or laterally. The spine was very rigid on attempt at flexion or extension, but otherwise negative.

Extremities: Marked diplegia of spastic type was noted.

Upper extremities: Attitude—the fingers were flexed on the hands, the hands on the forearms. The forearms were flexed on the arms and everted. Attempts at pronation and supination were difficult. Passive movements were resisted but were not painful. The pectorals were tense. Placed in extension, the arms gradually assumed the position described above.

Lower extremities: Very spastic and held in forced extension with the feet in equinovarus position. The Kernig sign was positive. The vasomotor system showed acrocyanosis. There was a general bluish mottling of the skin.

Reflexes: These were everywhere much increased. Dorsal flexion of great toes occurred on plantar stimulation. No clonus was elicited. No signs of inherited syphilis were found. The patient expressed no communication with the outer world, could not feed herself, see or speak, but cried a good deal when handled.

Laboratory Tests: Blood: Red blood cells, 4,190,000; white blood cells, 8,500; Differential: Polymorphonuclears, 64 per cent.; small mononuclears, 28 per cent.; large mononuclears, 7 per cent; eosinophils, 1 per cent.

The Wassermann test was negative.

The urine had a specific gravity of 1.008, was acid and contained a trace of albumin. Fehling's was negative.

The microscopic examination was negative.

The cerebrospinal fluid under pressure of 120 mm. was clear.

The white cell count was 2 per cubic millimeter. The Nonne, Noguchi and Fehling's tests were negative.

The Wassermann test in the spinal fluid was negative. The temperature varied between 97 and 100.5. The pulse ranged from 90 to 100.



Fig. 4.—Patient D. F., aged 4 years.

Generalized convulsions occurred about every week and lasted from three to five minutes. Twitchings, or rather tonic spasms of the quadriceps femoris, all the muscles of the shoulder girdle, arms, hands, and neck, developed and were continuous except during sleep. The introduction of stovain (1/30 gr.) into the subarachnoid space controlled the spasms for six hours. Finally the spasms of the masseters became so severe that the lower jaw was dislocated. Meantime dysphagia and marasmus became very marked, the temperature rose suddenly to 105 and the patient died, three years after the onset of the disease.

The brain alone was permitted to be removed at necropsy, three hours after death, by Dr. J. Oliver, whose studies on the pathology of this case are detailed hereafter.

The chief interest now centers itself about the etiology of this disease, which still is a matter of much discussion. Is the disease inherited or due to some inherent defect in the gray matter of the central nervous system, or, if acquired, is it due to some kind of degeneration? Pathologic studies alone can help us in this search.

Sachs thought the disease was due to "an arrest of cerebral development"—agenesis corticalis, as he called it. Others, including Kingdon,¹⁴ thought it an acquired disease, purely degenerative in character. Still others considered the changes due to certain toxins, syphilis or tuberculosis.

Sachs says: "A child to be afflicted with amaurotic family idiocy is born with a limited and restricted capacity for normal development. Its gray cells may do as well as any other child's up to 2, 3 or 6 months, but beyond that its powers for further development will not go." Therefore, he considers this disease a *congenital affair* in which, when normal development ceases, degeneration begins.

Hirsch¹⁵ emphatically is determined that its character is acquired, caused by toxemia.

In the case cited above a family history pregnant with nervous disorders (some of which might have been similar to the disease under discussion), alcoholism soon after birth, and later food poisoning were prominent features. Could not this child have had a nervous system which was fertile soil for the production of this disease by disturbed metabolism with toxemia produced by alcohol and food poisoning? Dixon and Cohen¹⁶ have tried to unite the inherited, toxic and degenerative theories advanced, and this case seems an ideal one, not only to justify a suitable explanation for its etiology, but to knit more closely the two types of this disease into one, namely, amaurotic family idiocy.

PATHOLOGIC REPORT

Few nervous diseases have received the careful study that has been given to the pathologic anatomy of amaurotic family idiocy. Though a comparatively rare disease, we know the structural changes which characterize the process so definitely that we may consider them pathognomonic of the disease. It is with some hesitation, therefore, that a detailed description of a new phase is given. Certain more unusual appearances have been met, however, which merit attention, and for the sake of completeness the entire findings have been given.

The literature of the subject has grown to such enormous proportions since the appearance of Sachs' original description³ that a

14. Kingdon: Tr. Ophth. Soc. United Kingdom, 1892, xii.

15. Hirsch: Jour. Nerv. and Ment. Dis., 1898, xxv, p. 538.

16. Cohen and Dixon: Jour. Am. Med. Assn., 1907, xlviii, 1751.

review of the subject is impractical. Among the pathologic studies Schaffer's,¹⁷ Vogt's,¹⁸ Spielmeyer's¹⁹ and Mott's²⁰ works are representative. We would, however, note the articles of Bielschowski,²¹ Frey²² and Schob,²³ who have paid particular attention to the changes in the cerebellum, as similar alterations were found in our case.

The necropsy was done by me two hours after death. The body was that of an extremely emaciated, fairly well-developed female child of apparently 7 years of age. There was a marked atrophy of the muscles of the extremities. The pupils were equal and dilated. No superficial enlargements of lymphatic glands were seen. The abdominal and thoracic cavities and their contents were negative, with the excep-

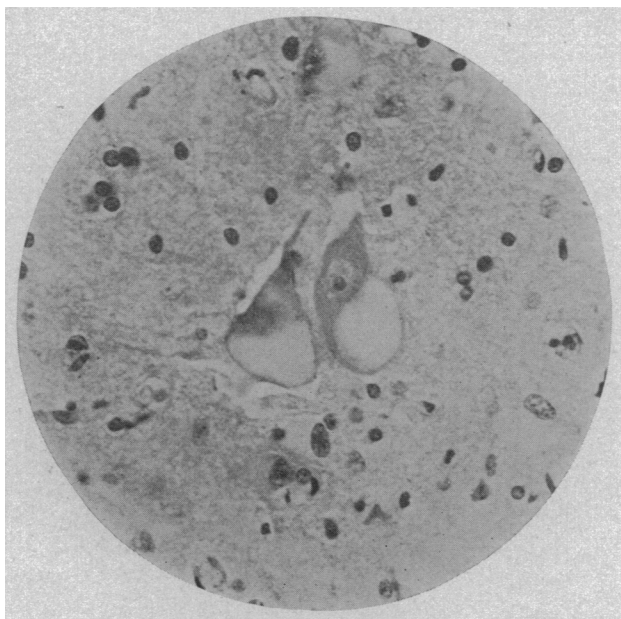


Fig. 5.—Precentral gyrus, Nissl stain. From photomicrograph. Two large pyramidal cells are seen with typical inflated areas. The nucleus of one is apparently normal. (Spencer 4 mm. Obj. Compens. Oc. 9x).

tion of a bronchopneumonia in the lower lobes of both lungs. The head was well shaped, and the skull of normal thickness and contour. The dura was somewhat loose, apparently normal, there being no remains of any old trauma from the difficult labor. The pia showed

17. Schaffer: *Neurol. Centralbl.*, 1905, xxiv, 386, 437.

18. Vogt: *Arch. f. Kinderheilk.*, 1909, li, 1.

19. Spielmeyer: *Histol. v. Histopath. Arbeit.* (Nissl), ii.

20. Mott: *Arch. Neurol.*, iii, 1907, 218.

21. Bielschowski: *Deutsch. Ztschr. f. Nervenheilk.*, 1913, 1, 7.

22. Frey: *Virchow's Arch. f. path. Anat.*, 1913, ccxiii, 308.

23. Schob: *Ztschr. f. d. ges. Neurol. v. Psychiat., Orig.*, 1912, x, 303.

a diffuse thickening over the anterior portions of the cerebrum, and over the base of the brain. The convolutions of the cerebrum were normal in arrangement, showing none of the abnormalities described by previous authors, such as, a communication of the rolandic with the sylvian fissure, a gaping of the opercula to show the insula, or irregularities in the anterior calcarine fissure. The gyri in the frontal regions were distinctly narrower than normal, and there was a consequent widening of the otherwise normal sulci. The hypophysis and large venous sinuses at the base of the skull were normal. The brain was hardened in 10 per cent. formalin, and gross frontal sections made. In none of these was any abnormality in the white or gray matter noted.

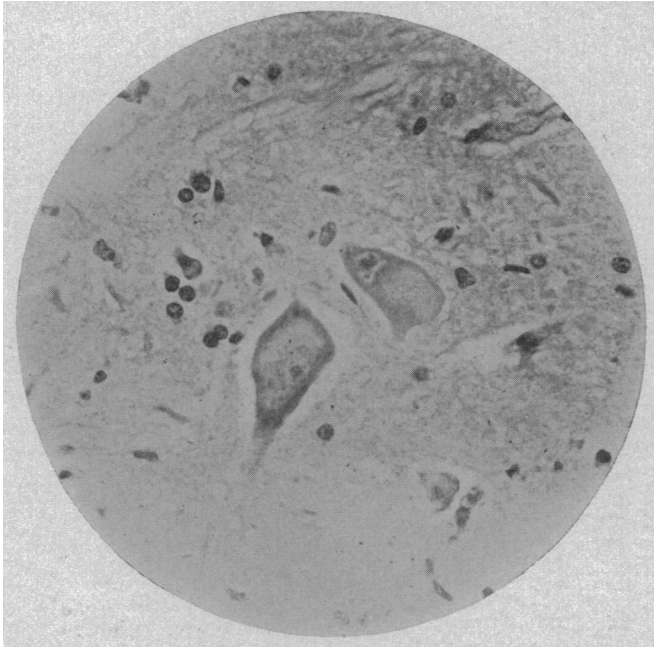


Fig. 6.—Anterior horn cells of cervical cord, Nissl stain. From photomicrograph. One cell shows the “inflated area” and in the other a small amount of the tigroid substance still persists in the neighborhood of the nucleus (Spencer 4 mm. Obj. Compens. Oc. 9x).

For microscopic study sections were prepared from various regions and stained with the Weigert-Pal, Nissl, Bielschowski and Mallory’s phosphotungstic hematoxylin methods.

Ganglion Cells.—The ganglion cells of the central nervous system, whether motor or sensory, showed the same type of lesion. The changes were especially well marked in the precentral gyrus (Fig. 5), the Purkinje cells of the cerebellum, the cells of the dentate nucleus and the anterior motor cells of the cervical cord (Fig. 6).

The changes consist in a solution or disappearance of the Nissl substance with an accompanying distention of the cell body at this point, so that the term "inflated" has been applied to describe the appearance. The lighter staining degenerated area thus produced in the nerve cell is filled with a delicate reticulum. The nucleus is, as a rule, displaced to one extremity of the cell and often shows pyknosis, though it may retain an apparently normal structure (Fig. 6). The disappearance of the tigroid substance begins in the neighborhood of the nucleus and extends gradually to the periphery of the cell (Fig. 5).

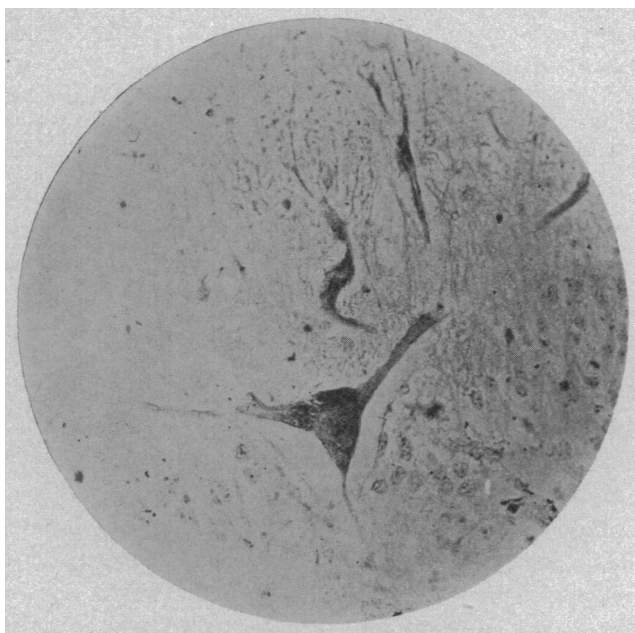


Fig. 7.—Purkinje cell of cerebellar cortex, Bielschowski silver impregnation. From photomicrograph. The upper part of the cell body is filled with deeply staining black granules. In the vertical dendrites are seen swollen areas filled with similar granules. (Spencer 4 mm. Obj. Compens. Oc. 9x).

The intracellular fibrils, as shown by the Bielschowski method, are entirely lacking in the "inflated" areas in the cell body, and persist only at the extreme periphery of the cell. The fibrillar structures of the dendrites and axons are as a rule normal.

The Sudan III preparations show the inflated areas of the affected cells to be filled with a fatty substance which stains a light orange-yellow. This lipoid material is very finely divided so as to give a ground-glass appearance rather than of separate droplets.

Somewhat different appearances are seen in the Purkinje cells of the cerebellum. Here the characteristic inflation of the cell body with

displacement of the nucleus is seen, but the process extends as well into the dendrites. On these structures are seen irregular swellings sometimes as large as the cell body itself. The contents of these protuberances are either clear and resemble the "inflated" areas in the cell body, in which case they may be shown to contain a fatty material, or they are filled with densely packed, silver-reducing granules (Fig. 7). Similar silver-reducing granules are seen in the cell bodies proper, and it would seem probable that they are of lipoidal nature. The axons, as far as they could be followed in the sections, were entirely normal.

The above described changes in the ganglion cells occurred with striking regularity throughout the entire central nervous system. There was, however, no marked decrease in the number of ganglion cells either in the cortex cerebri, in the Purkinje cells of the cerebellum or in the nucleoli of the brain stem. The arrangement of the layers of the cortex cerebri was still apparent, though somewhat indefinite on account of the marked degeneration of the constituent cells.

Medullated Fibers.—The Weigert-Pal sections show little change in the medullated nerve fibers as compared with the widespread change in their cell bodies. Sections of the cerebral cortex show a slight scarcity of fibers in the tangential layers, but the radial fibers show little if any change. A similar preservation of the medullary fibers is found in the optic nerve, olfactory bulb and in the optic chiasma immediately posterior to the decussation. In the cervical cord a few degenerated fibers are found in the lateral columns in the region of the crossed pyramidal tracts.

Neuroglia.—The neuroglia shows little evidence of proliferation in any of the regions examined. The greatest increase is found in the molecular layer of the cortex, especially in the frontal regions where the atrophy of the convolutions is most marked. Here a dense network of glia fibrils is seen, which is increased in thickness just below the pia.

Lipoids.—The subject of the lipoids of the nervous system and their "Abbon" products is too extensive to be thoroughly considered in this brief report. A brief description of the more important findings will be given.

The more universal stains for lipoids, such as Sudan III or Scharlach R, give the best general picture of the state of these fatty substances in the diseased nervous systems. The "inflated" degenerated areas in the ganglion cells, as described above, are filled with a fine granular fatty substance which stains a light orange yellow.

Scattered among the medullated fibers are other cells which contain rather larger deeper orange staining droplets in varying numbers.

The number of such cells varies widely in different regions, being especially numerous in the cerebellum. They are most likely the glia cells described by many authors (Merzbach, Alzheimer) as *Abraumzellen*.

Still other cells filled even to a greater extent with intensely staining orange red droplets are seen grouped around the perivascular lymph spaces. These cells are crowded with droplets of all sizes, so that their nuclei are obscured. These are the "adventitial cells" of Marchand, or in some part the emigrated glia *Abraumzellen*.

By means of the various differential stains for fat a rough micro-chemical determination of the nature of the fat can be made. It is found that the lipoidal substance in the degenerated ganglion cells is related to the phosphorus containing phosphatids or lipins (Leathes) of which the so-called "lecithin" is an example. The simpler fats, such as neutral fatty esters and fatty acids, are found only in the adventitial cells surrounding the perivascular lymph spaces. The glia cells show an indefinite intermediate reaction which may be interpreted as a midstage in the breaking down of the more complex lipoids. A large number of these glia cells contain double refractive fats, which give the typical "Maltese cross" with crossed Nicol's prisms. A small amount of such doubly refractive fats is found in the adventitial cells. It would seem most likely that in these anisotropic lipoids we have to do with cholesterin esters or cholesterin mixtures.

The chemistry of the brain lipoids is one of the most complicated fields of the biochemical sciences, and as our knowledge of micro-chemical reactions is very incomplete, it is difficult to draw any definite conclusions as to the chemical changes which are progressing in these diseased nervous systems. We are, however, warranted in saying that there is a demonstrable breaking down of the complex lipoids (phosphorus and nitrogen-containing lipins) into their simpler components (neutral fats, fatty acids and cholesterin compounds) and that the glia and adventitial cells play an important part in this process. It is interesting to note that Mott and others have described an increase in the cholin content of the blood in cases of amaurotic idiocy, so offering a possible explanation of the removal of the phosphorus and nitrogenous constituents of the lipins (phosphatids).

It is unlikely that the above described changes in the lipoids are in any way characteristic of amaurotic idiocy, for similar processes would be expected in all affections of the nervous system in which degeneration of nervous elements plays an important rôle. A further study of various degenerative conditions is in progress and will be reported in greater detail at a later date.

Pathologically our case agrees in all essential details with the reports found in the literature. We would call especial attention to the fact that there is an equal agreement with the descriptions of the infantile type of the disease. Sachs²⁴ in speaking of this relation says, "While there is a superficial resemblance between the cell changes in these two varieties of amaurotic idiocy, the differences are still more striking. In the juvenile form the disease is not so universal as in the infantile and we fail to find the typical balloon-like enlargement of the cell bodies and the swelling of the dendrites so characteristic of the cells of the Tay-Sachs type." In the present case of the juvenile type we find all these changes mentioned by Sachs.

It is interesting to note a recent study of an infantile case by Savini-Castano and Savini²⁵ in which a very extensive discussion of the etiology, pathogenesis and pathologic anatomy is given, with a review of the literature to date. Their findings are in a sense a reversal to the original conception of Sachs, in that they describe a "Bildungshemmung" of the myelinated fibers. They therefore consider the condition a degenerative process which has affected an undeveloped nervous system. This last they assume from the lack of differentiation in the layers of the cerebral cortex, the lack of differentiation of the various regions of the cortex, and the failure of myelination of the nerve fibers.

The present case, however, furnishes further confirmation to the conception that the disease is a degenerative process affecting a nervous system lowered in resistance or in vitality. As we have no morphologic evidence of congenital abnormality, either gross or microscopic, it would seem that it is the lowered vitality which is transmitted at birth, and these cells of weakened resistance suffer at a later date from the effects of some toxic agent as yet unknown.

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Other contributions to the literature on this subject are the following:

Sachs, B.: Jour. Nerv. and Ment. Dis., 1892, xix, 603.

Sachs, B.: Deutsch. Med. Wchnschr., 1898, xxiv, 33.

Jacobi: Arch. Pediat., 1898, xv, 561.

Holden: Jour. Nerv. and Ment. Dis., 1898, xxv, 550.

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24. Sachs: Jour. Exper. Med., 1910, xii, 685.

25. Savini-Castano: Ztschr. f. Kinderheilk., Orig., 1913, vii, 321.