Pathological Section.

February 7, 1911.[1]

Seven Cases of Amaurotic Idiocy (Tay-Sachs Disease).

By Hildred B. Carlyll and F. W. Mott, F.R.S.

PART I.—By Dr. Carlyll.

Amaurotic family idiocy is a name which has been given to a rare disease of the nervous system occurring in Hebrew children. For these reasons a practical knowledge of the disease, as regards clinical symptoms and diagnosis, can be possessed only by a few; and, further, the objection raised by the Jewish race to autopsies increases the difficulty of obtaining material for systematic pathological research.

The clinical symptoms of the disease are so characteristic that, if borne in mind, no difficulty in diagnosis should occur; indeed, the pathology is so distinct as to indicate a correct diagnosis.

In recent years, as knowledge of the disease has increased, many accounts of cases, partial or complete, have been published; so that a correct diagnosis is now arrived at more frequently. As yet, however, the majority of text-books contain no adequate account of this interesting disease. It is therefore with no apology that I put on record the notes of six cases which have come under my personal observation during twelve months' residence at the East London Children's Hospital, together with those of a case recently under Dr. Mott's care. That the details of some of these cases are incomplete will be evident to the reader, but I trust that the shortcoming may be condoned when it is remembered that in these alien families the details of the medical history had frequently to be obtained through an interpreter.

[1] Laboratory meeting held at the National Hospital, Queen Square.

My six patients are not akin to one another, but an elder brother of the first child whom I saw suffering from the disease had died three years before of the same complaint. His case, with another under Dr. Mott's care, was published in detail by Dr. Mott in the third volume of the *Archives of Neurology*, and I shall draw from the notes of that case for purposes of comparison with those of his sister (Case I). Case VII is a patient that recently came under the notice of Dr. Mott at Charing Cross Hospital, and, with his permission, I have included the history with my series of cases.

One of my patients (Case IV) came under observation in an interesting way. The mother of the two children mentioned above, a woman of unusual intelligence, noticed this child in his mother's arms in a tram-car. A rapid inspection convinced her that the child could not see, and she quickly came to the conclusion that his state was identical with that of her own children. The child's mother was so impressed with the statement that her baby could not see, which fact she had not discovered for herself, that she readily consented to bring him to the hospital.

The seven patients are all children of Jewish patients, coming from Russia or Poland. Some of the children were born abroad, others in England. Five cases are of girls, two of boys. Another member of the family of my first patient (Case I) died of the disease; and in Case III there are reasons to suppose that the only other child of that family may have died of the same affection. The youngest child in the family of which the patient (Case II) was a member presents certain very suspicious symptoms, and will be kept under observation.

All the children have now succumbed and their ages at death were as follows:—

Case I, 2 years 3 months.
,, Ia, 12 months.
,, II, 2 years 4 months.
,, III, 1 year 8 months.
Case IV, 2 years 3 months.
,, V,[1] 13 months.
,, VI,[1] 18 months.
,, VII, 17 months.

Dr. Mott's other case, reported in the third volume of the *Archives of Neurology*,[2] died at the age of 2 years.

In the light of these figures, and of those of other published cases, it is justifiable to tell the parents that children with this affection will not reach the age of 3 years. In none of the families from which these cases are taken is it recorded that the firstborn children were afflicted with the disease (except in Case III).

[1] These cases have died since this paper was written.
[2] *Arch. of Neurol.*, 1907, iii, p. 218.

In Case I and in Case 1A the fourth and fifth children of the family were affected.

In Case II the patient was the fourth child of the family.

In Case III the second child was affected (the first child is now known to have died from the disease).

In Case IV the patient was the second child of the family.

In Case V the fourth child was affected.

In Case VI the third child was affected.

In Case VII the seventh child was affected.

In every case (except Case III) the patient had healthy brothers or sisters.

In the case of Jenny M. (Case I) the mother sought advice as to whether she would be wise in having any more children or not. She was told there was no reason to believe that her next child would be afflicted.

Case I.—Jenny M.

Under the care of the late Mr. Hancock at the East London Children's Hospital, 1909.

Family history: Parents alive and well. They are Jews, the father coming from Russia and the mother from Poland. They reside in Spitalfields. No consanguinity. When married, father was 18 and mother 17 years old. The patient is the fifth child of the marriage. The eldest child died at 8 months, of diarrhœa. The second child is now 8 years old and is well. His eyes have been examined and nothing abnormal was detected. The third child, a girl, died of pneumonia when a baby. The fourth child, a boy, afflicted with amaurotic idiocy, died at Shadwell at the age of 12 months (Case Ia). The fifth child is the patient. No miscarriages. The parents have decided not to have any more children.

Mother's family: The mother's parents are alive and well. No consanguinity. She is one of seven children, of whom three are dead, the cause being unknown. One of her brothers is married, but has no children; her other brother has had four children, who are all healthy.

Father's family: There is no information about the father's grandparents; his parents are alive and well. No consanguinity. He has two brothers and seven sisters; of the latter, one died at the age of 3 years from croup, and one after living a few weeks. The remaining five are between 12 and 22 years of age; they are healthy; none are married. Of the two brothers, one is married and has two children who are well, the other is 6 years old.

History: Full-time child, no instruments; breast-fed up to eleven months. The mother, a very intelligent woman, brought her to see Mr. Hancock when she was 4 weeks old because she thought the child was "going like Jack." When the child was 3 months old the mother brought her again, as she noticed that she was partially blind. (Mr. Hancock found the typical ophthalmoscopic signs.) She noticed also that the limbs were stiff because she had difficulty in powdering the groins. The child cried less than other children and did not take any notice of things. From birth she never recognized the difference between the mother who nursed her and other people who lifted her up; nor did she ever play with toys. The general health for twelve months was fairly good, but gradually she got thinner and took her food badly. She always lay quietly where she was put, and the power in her limbs rapidly decreased.

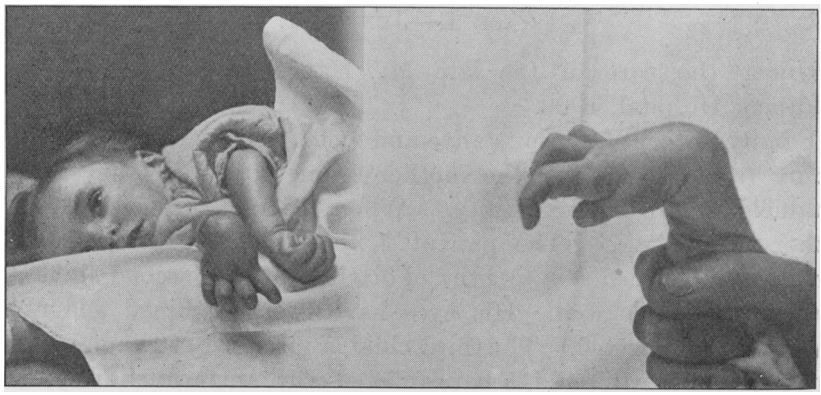

FIG. 1. Case I.—Jenny M. FIG. 2.

July 9, 1909. July 9, 1909. Showing the early "main en griffe."

On admission, January 9, 1909, aged 1 year and 4 months (the following meagre notes are all that are obtainable): Well nourished and plump. Takes very little notice of people or surroundings, and appears only to eat and sleep. Heart and lungs normal. No convulsions. No strabismus nor nystagmus. Limbs spastic. Weight, 19 lb. 11 oz.

Progress: There are, unfortunately, no notes about her progress; but I am told that the child became progressively thinner, and that nasal feeding became necessary about May. In July, her weight was 14 lb., and the photographs taken then show the hyper-pronation of the left

forearm. On the right side, the hand has assumed a position of "main en griffe" (figs. 1 and 2).

November 9: Always lies in a semi-comatose condition; eyes continually open; pupils dilated, reacting slightly to a strong light. The eyelids sometimes blink, and the eyes are at times withdrawn from a bright light. Optic atrophy marked. Usually there is a slight internal strabismus of recent date. The mouth is kept shut, but can be moved well. There is a slight sucking reflex. The child seems insensitive to sound; head retracted; back considerably bent with scoliosis and kyphosis. Right side: Arm kept slightly from the body and extended at elbow; forearm fully pronated; wrist acutely flexed, and has sore places on dorsum. Fingers hyper-extended at metacarpo-phalangeal

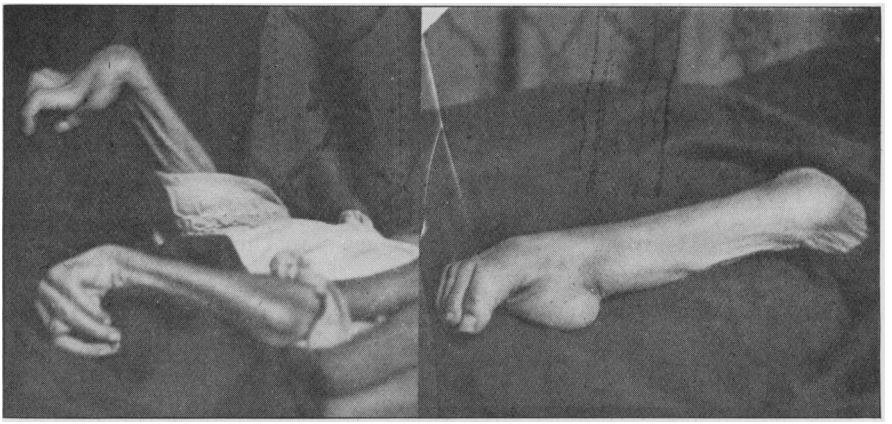

FIG. 3. Case I.—Jenny M. FIG. 4.

November 12, 1909 (a few hours before death). Note the difference in the deformity of the two limbs.

November 12, 1909.

joints, and flexed elsewhere; thumbs fully adducted and slightly opposed; slightly flexed at metacarpo-phalangeal joint and extended at the inter-phalangeal joint. Leg flexed at hip and knee; sores present over knee; foot and toes plantar flexed to the fullest extent. Left side: Arm slightly flexed at elbow; forearm hyper-pronated; leg straight at hip and knee; position of foot as on right side. These contractures are well shown in figs. 3 and 4. Abdomen very lax; no enlargement of liver or spleen. The plantar reflex is extensor on each side, as exemplified by a slight straightening of the great toe. Deep

reflexes not obtained. There is great muscular wasting. The position of the joints can be altered by force, but they tend to return to the original position, except in the case of the right knee, the muscles of which are very weak and lax, so that the joint can be placed in any normal position. There are numerous pressure sores all over the body. Urine and fæces are passed in the bed. Nasal feeding has been employed for five or six months. There have been several slight attacks of bronchitis. The temperature has been normal throughout, except for some terminal pyrexia.

November 12, 1909: The child died, aged about 2¼ years.

Immediately after death had occurred the eyes were removed and placed in fixing solutions. The brain was removed later and hardened in Müller's fluid, and subsequently examined by Dr. Mott. No further examination was permitted.

Case Ia.—Jack M.

This child was under the care of Dr. Eustace Smith, Dr. Coutts, and Mr. Hancock at the East London Children's Hospital, in 1906. Dr. Mott performed the autopsy, and has published the result of his chemical and histological examination in the *Archives of Neurology*, iii, 1907. With his permission, and as the second case in the family (Case I) has recently proved fatal, I give his notes here for comparison :—

Family history: *See* Case I.

History: Quite healthy at birth. Normal confinement. No urine passed for twenty-four hours. When six months old the child developed a rash which lasted four or five days. Soon afterwards he developed pneumonia, being dangerously ill for a week. Since this illness he has not noticed things, and his mother thinks this may be due to deafness. His attention cannot be attracted. The eyes wander aimlessly. The mother thinks he should hold his head up better for his age. He has had an aural discharge for five months. No squint. Breast-fed always; no other food; bowels regular. Has never walked nor crawled, but at 6 months old could stand firmly on his legs when allowed to do so. No definite paralysis. The back muscles appear to be quite strong. At six months old the child was taken to the Moorfields Eye Hospital. He was admitted, but having contracted measles, was discharged shortly afterwards.

On admission, January 13, 1906, aged 8 months: Weight, 20 lb. 10 oz. Very well nourished, rather pale. Head of good shape; fontanelle widely open; no cranio-tabes; hair normal. Eyes wander

aimlessly. Attention appears to be attracted, however, by the ticking of a watch, and he looks for it in the right direction. When placed in a sitting position his head does not fall about. Muscular development appears to be very good. Skin normal. Sleeps and eats well. A very amiable child. Gastro-intestinal system: Two lower incisors only; tends to protrude tongue like a Mongol. Abdomen large; spleen and liver not felt. Bowels usually regular; stools normal. Thorax: Well covered, good shape; nothing abnormal in heart or lungs. Nervous system: Cranial nerves intact; pupils equal in diameter; normal reactions direct and consensual; eye movements good in all directions; no nystagmus nor strabismus; no paralysis nor muscular wasting. Reflexes normal for child's age. Fundi present characteristics of the disease.

Discharged January 25, condition "in statu quo."

Re-admitted February 7, 1906, suffering from pneumonia, following what was said to have been measles, but which was probably scarlatina. Very weak. Still well nourished. Neck muscles now obviously weak, causing head to fall back; no rigidity; no obvious muscular wasting; reflexes are still brisk; plantar reflex extensor; eyes are unchanged; well-marked signs of broncho-pneumonia.

February 18: Has been in a critical condition, but signs in lungs are now clearing up. Reflexes brisk. Head muscles weaker, but can move head a little from side to side.

February 24: Still some bronchitis. Right arm now appears to be rigid. Desquamating freely.

February 26 to March 10: Temperature is very irregular, reaching 103° F. at times. Losing weight (14 lb. 14 oz., March 8). Well-marked œdema of hands and feet; semi-conscious. Rigidity of limbs variable. Resents ophthalmoscopic examination.

March 31: Weakness increasing. Temperature subnormal. Profuse hæmaturia. No casts in urine.

April 10: Marked anæmia; skin very dry. Much œdema; abdomen very sunken; skin loose and inelastic; has fits of crying and irritability. Does not know anyone; no hæmaturia; rarely moves limbs, and then only the upper; no vomiting. Eyes nearly always open; they wander aimlessly. Limbs alternately rigid and flaccid. Lower limbs powerless; knee-jerks brisk; Babinski's sign variable.

April 12: Child died suddenly, aged 12 months.

Case II.—Milly T.

Under the care of Dr. Eustace Smith in the East London Children's Hospital in 1909. Died at St. George's Infirmary, E., 1910. No autopsy.

Family history: The parents are Russian Jews, and have been in England seven years. They are both strong and well. They have had five children, three older and one younger than the patient. The older children are boys, aged 12, 10, and 5 years respectively (1910). The youngest of the family is a girl aged 8 weeks. I have recently seen this child, and she presents a suspicious similarity to early sufferers from amaurotic idiocy. I was not given permission to examine her eyes. There is no consanguinity between the parents. When they married the mother was aged 20 and the father 24. They do not know of any similar cases of illness in their respective families.

The patient was born at full term without the assistance of instruments, and was brought up on the breast and the bottle.

History: The child was quite well until a year old, when she seemed not to see, and was taken to a hospital. She seemed to notice only bright lights, and could not support her head. At 3 months old she had fallen on her head. Is usually constipated, and has been wasting latterly. Has had no infectious fevers.

Admitted July 8, 1909, aged 16 months. Well developed and well nourished. Skin pale. Weight, 16 lb. General muscular rigidity, especially in arms and legs, which are slightly extended. This stiffness is easily overcome. No head retraction or spinal rigidity. Child lies in a restless condition. Eyes rather fixed, and kept open. Sight seems impaired, but she is not blind, for she turns eyes towards objects presented. (There is no note of an ophthalmoscopic examination.) Cranium well shaped; anterior fontanelle almost closed; no cranio-tabes. Nostrils triangular shaped. Mouth kept open; tongue protruded and often sucked. Abdomen protuberant and rather flaccid. Liver and spleen not palpable. Knee-jerks decidedly exaggerated. No ankle-clonus. Plantar reflex extensor. Lungs and heart normal. Child swallows badly.

Discharged July 14, 1909. Whilst under observation, the temperature ranged continuously from 100° to 102° F. Lumbar puncture revealed a sterile fluid containing a few lymphocytes.

Admitted to infirmary, October 25, 1909, aged 19 months. Weight, 18 lb. 10 oz. The pupils were small and reacted. There was apparently no sight. The face twitched symmetrically. Kernig's sign was marked. There was much salivation.

November 13 : Weight, 18 lb. By the kindness of Dr. Bowlan I was allowed to watch the child's progress.

December 8 : Weight, 17 lb. The child lay where placed, but started at sudden noises. Pale and flabby, features becoming pinched. Much crying. Swallowed fairly well, and did not require nasal feeds. Head fell back when child lifted. Limbs slightly rigid. Knee-jerks brisk. Plantar reflex extensor. Thumbs markedly adducted. Examination of the fundi revealed the characteristic appearances. Lumbar puncture gave a small quantity of fluid under very low pressure. Shortly after this child became worse, limbs being much contracted. Nasal feeds became necessary for a time.

December 26 : Weight, 16 lb. 8 oz.

January 3, 1910 : Weight, 16 lb.

January 12 (*see* fig. 5) : Swallowing well. Pupils react to light. Limbs not markedly contracted, but both hands clenched over adducted thumbs. Plantar reflex indefinite but not extensor. A quantity of fluid was obtained by lumbar puncture.

FIG. 5.
January, 1910. Case II.—Milly T.

The child stayed in much the same condition for several months, becoming more wasted and rigid.

The cerebrospinal fluid (first sample) was alkaline and contained some sugar. Noguchi's test showed an absence of globulin. There were neither cells nor organisms present. Second sample : Protein content normal. Choline test negative. No lipoids beyond a trace of cholesterol present.

July 18, 1910 : Death occurred from pneumonia, following an attack of measles, at the age of 2 years 4 months. No autopsy was allowed, in spite of the most urgent appeals for permission.

Case III.—Fanny M.

Under the care of Mr. Hancock at the East London Children's Hospital for a short time. Transferred, on account of an epidemic of measles, to the Evelina Hospital in 1909, where she was under the care of Dr. Briscoe. (Owing to Mr. Hancock's death, the child's condition while at Shadwell is not known.)

Family history (1910): The mother was married once previously in Poland when she was 16 years old. Of this marriage she had one miscarriage. She was aged 24 when she married, in 1904, her present husband. He was 30 years old. No consanguinity. They are Polish Jews, and have lived in England for five years. The mother's parents died when she was a baby. She has one brother, aged 35, who has six healthy children. The father has one sister and several brothers, who have healthy children. The parents have never seen any children with amaurotic idiocy in Poland. They have had two children in all; the first, a boy (J. M.), was born in Poland, and died in 1907 at the German Hospital, aged 2¼ years. The case-notes are not obtainable. He was weakly from birth, and said to be rickety. Breast-fed for twelve months. Never used his legs. Became very thin before death. I have seen two photographs of this child, taken at 3 and 12 months respectively. The first photograph shows a fat, intelligent-looking baby with widely open eyes. In the second he is also fat, but presents a rather idiotic look. The limbs appear normal. The mother cannot say anything definite as to his powers of vision, but I think it probable that this child was an amaurotic idiot. The mother agrees that this is probable. (A recent examination of the sections which were prepared when this boy died, leave no doubt that he died of this affection.)

History: Born in England at full term; large child at birth; no instruments. Breast-fed to 8 months. Well up to 6 months, when she became weaker and could not hold up her head. When about 8 months old it was noticed that she did not observe things like other children. Sudden noises would start "convulsions."

General condition: The child was sent to the Evelina Hospital on October 7, 1909. She was then 18 months old. Mr. Hancock was anxious to know how she progressed, and I was very kindly allowed to examine her there on November 23, 1909, when her condition was as follows: The face presented a look of dementia, and the child lay where placed. There were no voluntary movements, even when lumbar

puncture was performed; nor did the child cry. No obvious muscular wasting and no contractures were observed. The arms and legs were extended and slightly rigid, but flexion could be performed. Thumbs markedly adducted. Some foot-drop, but this was not well marked. Extensor plantar reflex well marked on each side. Knee-jerks obtained, but not exaggerated. Eyelids sometimes open; no movements of eyes; complete blindness; well-marked optic atrophy. At the macula was a circular area rather larger than the disk, of the colour of dirty cotton-wool, with an ill-defined edge. In the centre of this area was a well-marked liver-coloured spot. The child on admission had taken food fairly well, but for some weeks past had been fed by a nasal tube. Lumbar puncture was readily performed. There was no vertebral

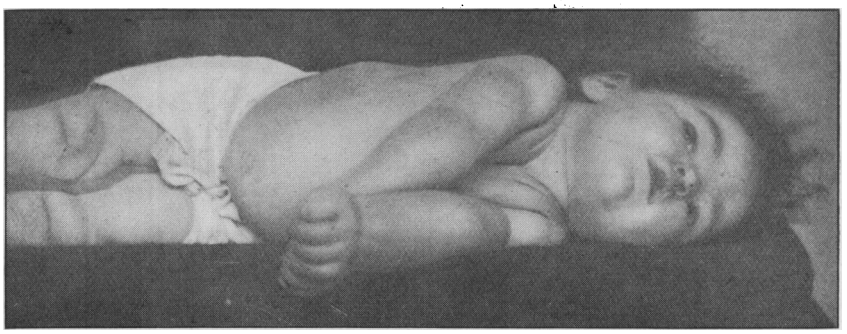

FIG. 6.

Case III.—Fanny M.

rigidity. Two large test-tubes were rapidly filled with clear fluid. Shortly afterwards the child developed chicken-pox, and on December 20, 1909, she died, aged 1 year and 8 months. I was told that no improvement had followed the lumbar puncture (fig. 6). The specimen of cerebrospinal fluid was free of blood, and was not abnormal in cell-content. Reaction alkaline. Noguchi's test showed that it contained no globulin. With Fehling's solution a rapid reduction took place, as is usual with normal cerebrospinal fluids. There was but a small amount of protein. Choline and cholesterol were absent.

Post mortem (December 22, 1909): Well-nourished child. Fontanelle closed. Brain very hard; weight, 33 oz. Ventricles not distended, but a quantity of fluid escaped on opening the skull cavity. Some pus was found in the right pleural cavity.

Through the kindness of Dr. Briscoe, I was enabled to be present at the autopsy, and to obtain portions of the nervous system and other tissues for pathological research. This was carried out under Dr. Mott's direction, and a portion of the histological and chemical investigations are based upon researches made upon this material (*vide* Part II).

Case IV.—Abraham C.

Under the care of Dr. Eustace Smith in the East London Children's Hospital, Shadwell, 1908 and 1909. Death occurred in the St. George's Infirmary, E., 1909. No autopsy.

Family history, 1910: Two other children, one aged 6, healthy and at school; the other died of "cough" at 2 weeks old. No miscarriages. The parents come from Russia and have been ten years in England. When they married the mother was aged 20 and the father 22. The mother's parents are alive and well. She has three brothers, aged 12, 10, and 6 respectively, and four sisters. Of these two are married and two are still young. Of the former one has two girls and one boy; the other has one girl. The father's parents are alive; he has brothers and sisters, but nothing is known of them.

History: Full-term child; breast-fed; no instruments. At 3 months old suffered from cramps and constipation; occasional fits. Irritable for two months and suffered from screaming attacks. For two months previous to admission mother had doubted whether he could see properly. A diagnosis of rickets was made at several hospitals.

Admitted to the East London Hospital, October 30, 1908, for bronchitis. Aged 1 year. Weight, 22 lb.; very rickety and unable to stand. Well covered with flesh. Irritable and cries a great deal. Occasional nystagmus; unable to fix objects with eyes. Characteristic appearances seen in fundi. Limbs flaccid. Both knee-jerks brisk. Sometimes a slight ankle clonus occurs. Plantar reflex extensor. Fontanelle normal for age. Liver and spleen not palpable. Four central incisors, two upper and two lower appearing.

Discharged November 9, 1908.

Re-admitted January 30, 1909, for bronchitis following a recent attack of measles. Weight, 15 lb. Child apparently quite unconscious. The only movement is a slight slow rolling of the head from side to side. Slight general rigidity. Eyes half-closed, exhibiting slow lateral conjugate movements; pupils small, equal, and circular; no nystagmus; optic atrophy. Abdomen flaccid and retracted. No œdema.

February 3: Lumbar puncture was followed by a slight improvement. The fluid was sterile and showed a few small lymphocytes, but not in pathological numbers.

February 9: Sometimes swallows naturally but generally requires nasal feeds.

February 19: Gaining weight; total weight now 18 lb. Nasal feeds not required.

Discharged March 8. Some improvement.

Re-admitted October 1, 1909, for the third time. Weight, 20 lb. Has taken food well since last admission. Very constipated. Feet and abdomen said to have recently swelled. Fairly well nourished. Lies on side with head retracted. Eyes open and staring. When disturbed eyes move ceaselessly from one side to the other side with rapid, jerky

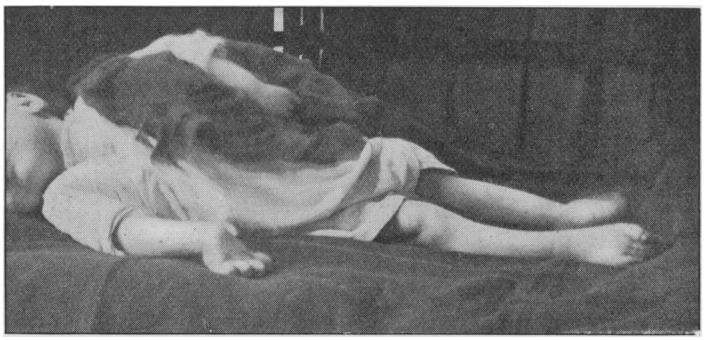

FIG. 7.

October, 1909. Note the claw hand. Case IV.—Abraham C.

movements. Pupils do not react to light. Legs extended at knee and ankle, but slightly flexed at hip-joints. Plantar reflex flexor; the stimulus usually gives rise to slight clonic spasm of arms and legs, as does any movement of the legs. Knee-jerks increased. No genuine patella or ankle clonus. Arms slightly flexed at elbows; wrists flexed; claw hands. Joints are resistant to passive movement, but on continuing it they become relaxed, and complete flexion and extension can be obtained. The usual position of the joints is, however, quickly resumed (fig. 7).

Discharged October 17, 1909.

Admitted November 2, 1909, to the St. George's Infirmary. By the courtesy of Dr. Bowlan I was permitted to examine the child on

December 8. Shortly after admission he had convulsions associated with œdema of the legs. He swallowed well and cried but rarely. It was thought that at times he recognized his mother. The head and arms could be moved by the child. The legs were kept extended and rigid. Plantar reflex flexor. Kernig's sign not marked. Well-marked "claw" position of right hand only. Thumbs on each side much adducted and opposed. Eyes showed bilateral movements. Lumbar puncture was performed, but the fluid was not found to be under any pressure. It contained some blood, was alkaline, and contained sugar. Choline and cells absent.

Death, Christmas, 1909. Age about 2¼ years.

Case V.—Harry K.

Under the care of Dr. Coutts at the East London Children's Hospital, 1910.

Family history: The parents are Russian Jews and are alive and well. They were not related before marriage. They came to England in 1903. There are three other children, a boy and two girls, aged 8, 5 and 2½ years respectively; all alive and well. No miscarriages. The father is one of seven children; his parents are alive. The mother is one of four children; her parents are dead. I can find no evidence pointing to other cases of the disease in this family.

History: The child was born at full term and without difficulty. He was brought to Hospital because his back was weak, and because his mother thought he was "not like other children."

On admission, July 12, 1910, aged 9 months: Weight, 17 lb. Well nourished; pale; does not look intelligent. Fontanelle not closed. Plenty of hair. Circumference of head 18½ in. Has difficulty in sitting up. Is at times sensitive to sudden noises. Takes food well. Nothing abnormal in chest. Abdomen full and lax; nothing abnormal felt. No teeth. Long eyelashes. Cranial nerves intact. Eyes of oval shape, usually open and staring; no lateral movements; no strabismus. The fundi present a typical picture. The pale area at the macula is about one and a half times the size of the disk. Optic disks show early atrophy (Mr. F. Juler). The arteries are small. The pupils react strongly to light. The child sees objects and follows them with his eyes, but has no sense of their position when trying to grasp them. There is no head retraction, but the neck muscles are very weak. The legs are extended and are spastic, but not markedly so. Knee-jerks very brisk. Kernig's

sign indefinite. The feet go into clonus on stimulating the soles, but the legs are only sluggishly moved. The arms move freely at will, the elbows are rigid and flexed. A Pirquet's reaction was positive.

July 20: A test-tubeful of fluid, flowing under considerable pressure, was removed by lumbar puncture. A specimen of blood was removed from the brachial vein.

July 25: There was no pyrexia after the lumbar puncture, but the rigidity was for a time less marked. The operation wound on the arm healed by first intention. The cerebrospinal fluid showed an absence of choline and cells. There was no excess of protein. The amount of

FIG. 8.

July 19, 1910. Case V.—Harry K.

carbonates and carbon dioxide in solution was not altered. Cholesterol was absent. There was no excess of lipoids or fats.

August 26: Weight, 16 lb. Temperature normal. The child lies precisely where it is put, however uncomfortable the position. He is almost ridiculously good for his age, rarely crying, and then only on the greatest provocation. He usually looks about him with widely open, staring eyes, which produce an absurdly vacant expression. He grunts with pleasure when he is spoken to, and frequently bursts into laughter. It is evident that he does not recognize his mother. Perception of light and of bright objects is fairly keen. No squint nor nystagmus; pupils

react strongly to light. Mouth almost always open; tongue is protruded sometimes. On being sat up, the weakness of the back muscles is evident; but if the head is pushed backwards, as it is very readily, the child can bring it forward to a flexed position. The arms are flexed at the elbows, and are constantly moving. The forearms are strongly pronated. The thumbs are adducted and opposed, and the fingers are kept flexed. Legs somewhat spastic; knees kept extended; thighs are adducted and forcible abduction causes pain and reveals the muscular rigidity. The plantar reflex is flexor; knee-jerks easily obtained, but not very exaggerated. The legs are not moved away from painful

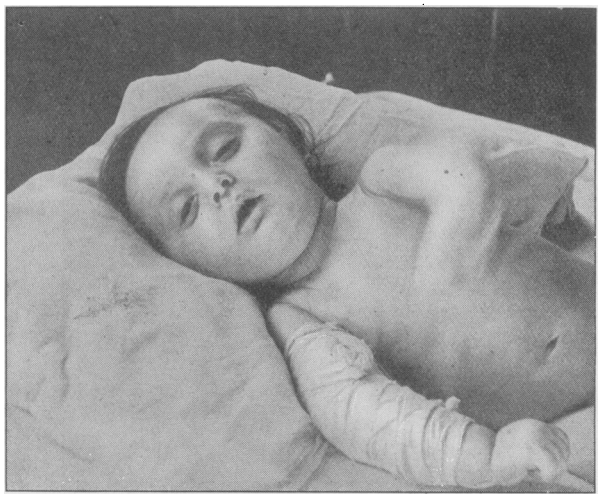

FIG. 9.

July 28, 1910. Case V.—Harry K.

stimuli; they fall helplessly on being lifted. The child takes food well, but will not be bothered with a bottle. The bowels are regular; stools and urine normal. (*See* figs. 8, 9, and 10).

October 1: Weight, 14 lb. 12 oz. Hands pronated and thumbs tucked in. Fingers move readily at will. Knees extended; no equinus; plantar reflex flexor; jerks readily obtained. There is some difficulty in swallowing at times, but nasal feeds are only occasionally needed. The child has no teeth. The general weakness has increased. On placing salt upon the tongue the child does not cry, but makes a slight grimace.

At times there are outbursts of vacant laughter. Pin-pricks do not readily cause crying. The pupils react slightly to light.

The child was removed by the parents from the hospital on October 31, 1910. Weight, 14 lb. The child died suddenly on November 4, 1910, possibly from some accident while being fed. No autopsy was permitted.

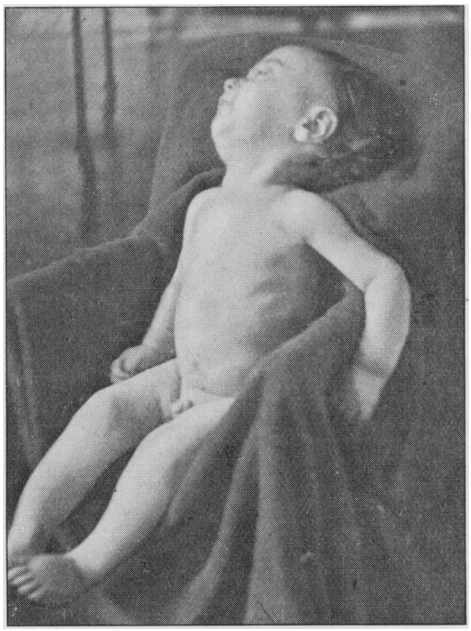

FIG. 10.

August 24, 1910. Note the results of weakness of the neck muscles. Case V.—Harry K.

CASE VI.—SARAH G.

In the Queen's Hospital for Children, 1910, under the care of Dr. Bellingham Smith, to whose courtesy in allowing me to admit the child for a time in the East London Children's Hospital, and to photograph her, I am much indebted. (This child was shown at the Royal Society of Medicine by Dr. Bellingham Smith in May, 1910.)

Family history: Patient is the third child of Polish Hebrews. The parents are alive and well. They were married in 1902, and have lived

in England for five years. No miscarriages. According to the history, the two elder children, a boy and girl, aged 7 and 4½ years respectively, are both healthy, and this is corroborated by a photograph of them which I was shown. The father is one of seven children, two of whom died in early childhood. One of his brothers is consumptive. He has a step-brother and four step-sisters. The mother is one of eight, of whom one died at the age of 3 years. Two of her brothers have two children each, but she is unable to say anything as to the state of their health.

History: The child was brought to hospital for blindness and inability to sit up. She could not hold up her head. She has always been breast-fed. The symptoms had only been noticed for a month prior to admission, namely, when the child was 10 months old.

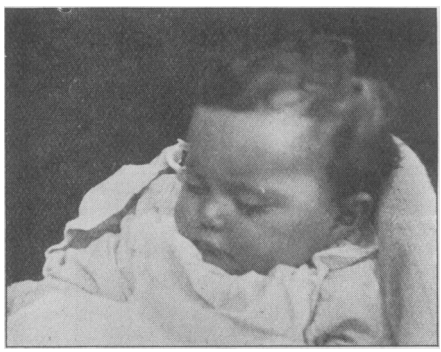

FIG. 11.

July, 1910. Case VI.—Sarah G.

On admission, April 27, 1910, aged 11 months: The child is exceedingly fat and well nourished; very apathetic; unable to sit up without assistance, but on doing so, is unable to support her head unaided. No movements of head or body are attempted, and those of the limbs are limited in character. The limbs are rigid to a variable degree, spasticity being more marked in the legs than in the arms. Plantar reflex flexor. The tongue is protruded. The appearance of the eyes is typical on ophthalmoscopic examination. Optic atrophy is fairly advanced, and the pale area at the macula is rather larger than the disk. There is no nystagmus, but the eyes exhibit aimless random movements. There is distinct appreciation of a strong light, but no notice is taken of surrounding objects. The Wassermann reaction and the Pirquet cutaneous reaction were negative.

July 18, 1910 (*see* figs. 11 and 12): Age, 14 months old; weight, 17 lb.; very plump; has two lower incisors; limbs very spastic; legs and arms being about equal in this respect; unable to sit up; plantar reflex definitely flexor; pupils do not react to light. After a lumbar puncture, at which some cerebrospinal fluid under pressure was removed, there was a pyrexia. The rigidity did not in any way decrease. Perception of light is slight. The pale area at the macula is smaller, and the liver-coloured spot larger than in Case V.

The child died in the autumn of 1910.

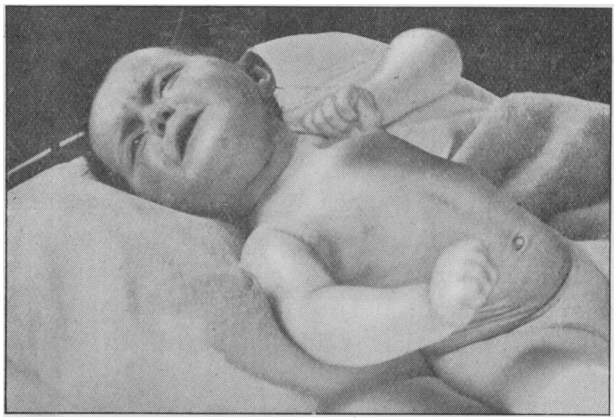

FIG. 12.

Case VI.—Sarah G.

CASE VII.—P. P.

Female, aged 1¼ years. Admitted to Charing Cross Hospital under the care of Dr. Hunter for broncho-pneumonia and rickets, May 25, 1910. It was thought the child did not see properly, and amaurotic idiocy was suspected. Mr. Treacher Collins made an examination of the eyes, with the following result: "Around each macula there is a circular area of white opacity on the retina. The macula itself appears as a dark red spot. The margins of the optic disks are well defined, but they are pale, especially on outer side. The case is one of so-called amblyopic idiocy met with in Jewish children" (E. T. C.)

The case was then transferred to the care of Dr. Mott. The mother, a Polish Jewess, who could speak only broken English, gave the following history: The child has been ailing for about four months with

frequent colds and a cough. A week ago the cough became worse. During the last two days the child has been drowsy and partly unconscious at intervals; she has also had twitchings in the arms, and at times gives sudden jumps. There has been no diarrhœa or vomiting, and food has been taken well.

Family history: The following history and pedigree were kindly obtained by Dr. Rees Thomas. Patient is the youngest child of a family of seven. There is no family history of asthma, consumption, epilepsy, insanity, or rheumatism. No case of blindness occurred in any of the children that died young, but the first two children (girls) both died at the age of 1 year from pneumonia, and it is possible that they were afflicted with amaurotic idiocy which, as in this case, was not detected. The third child, a boy, died at the age of 2 years from measles. The other three children, one boy aged 6, and two girls aged 4 and $2\frac{1}{2}$ years respectively, are alive and healthy.

On admission: The child lay in a semi-comatose state, slightly cyanosed, and took no interest while it was being examined; it neither cried nor struggled. Conjunctival reflex was very dull. Its hands and feet were cold. Respirations 70, pulse 170, temperature 103·4 F. Breath-sounds very harsh, and in patches bronchial in type. Moist râles, bronchi and crepitations could be heard. Abdomen lax. Head not retracted.

The physical condition of the patient improved under treatment. Its appetite never seemed to be satisfied; it was always crying, but upon giving it milk the crying would cease. It certainly heard loud noises, but exhibited no signs of disgust when medicine was given. Death occurred on July 17, 1910, and the autopsy was made by Dr. Mott.

Post-mortem notes: Physiognomy indicates no degeneration, like that of an idiot or imbecile. Palate shows no abnormality, broad and flat. Two central incisors, upper and lower, cut. Lower incisors notched, but certainly not indicative of congenital syphilis. No bruises or rashes. A little lividity of dependent parts. On opening chest and abdomen there were no adhesions or fluid. No fluid in pericardium. Slight beading of ribs. No indication of rickets in legs. Fontanelles still open. Tongue, fauces, tonsils, and larynx normal. Muscles good colour. Lungs: Some congestion of both bases. Heart apparently normal. Liver pale and mottled, suggestive of fatty change. Spleen normal. Adrenals small and pale. Kidneys rather paler than normal. Mesenteric glands: A few slightly enlarged; large gland near cæcum. Brain weighs 970 grm.: right hemisphere, 435 grm.; left hemisphere, 435 grm.;

pons, &c., 100 grm. No excess of fluid. No flattening of convolutions; decidedly firmer to touch than normal, has a leathery feel. Meninges not thickened; convolutional pattern complex. Sylvian fissure horizontal. Portions of the organs and the brain were removed for microscopical and chemical examination (*vide* pp. 188).

Historical Summary.

It was in 1881 that Waren Tay, of the London Hospital, discovered this disease, and his description of the ophthalmoscopic appearances, which has now become historic, may be read in vols. i and iv of the *Transactions of the Ophthalmological Society*.[1]

Under the heading, "Symmetrical changes in the region of the yellow spot in each eye of an infant," he says that in a child aged 12 months he found "the optic disks apparently quite healthy; but 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 in its centre a brownish-red, fairly circular spot, contrasting strongly with the white patch surrounding it. This central spot did not look at all like a hæmorrhage, nor as if due to pigmentation, but appeared to be a gap in the white patch through which one saw healthy structure. In fact, the appearances may most suitably be compared with those we are familiar with in cases of embolism of the central artery of the retina." In a note made five months later he adds that "the disks are undoubtedly becoming atrophic."

The disease was named "amaurotic family idiocy" by Sachs in 1887 [11]. Twenty-eight of his cases occurred in fifteen families, and extensive degeneration of the cortical pyramidal cells was described. A few years after Sachs' publication, Hirsch found the same changes, not only in the cortical grey matter, but also in the grey matter of the entire central nervous system, including the spinal ganglia; and these observations were confirmed by Sachs in 1903 [12].

Further corroboration was brought by Schaffer in a recent study of eight cases [14]. The name Tay-Sachs disease, by which it is sometimes known, was proposed by Higier, and in 1908 Apert collected 106 cases, of which seventy-three occurred in twenty-five families [2]. The observation that the disease is confined to Hebrews was made by Carter [3]. There is abundant evidence to prove that the retinal changes are not present at birth.

[1] *Trans. Ophthalm. Soc., U.K.*, 1881, i, p. 55; 1884, iv, p. 158.

In a case reported by Koller [7], a child aged 2 months showed signs of muscular weakness; but no unusual appearance was seen except an indistinct brownish patch at the foveal spot in one eye.

In 1894, Kingdon published a case of a child aged 9 months, who showed the typical ophthalmoscopic appearances [5]. He had examined this child when it was 3 months old, and when muscular weakness was commencing. The fundus was then normal. At a second examination, when the child was 5 months old, there was a suspicious haze at each macula.

Children affected with this disease as a rule succumb at about 2 years old, but cases have been recorded of children who lived for some years longer. Sachs is surely unduly careful when he says that the disease is "generally fatal" [13]. One of his cases was $5\frac{1}{2}$ years old, and Koller [7] has recorded a case of a patient who had optic neuritis at the first examination at 2 years of age, and who when nearly 4 years old could crawl about and mutter a few words. In the region of the macula there was "a slight veil-like, milky-bluish haze, gradually fading into the colour of the surrounding retina. In the centre of the opacity at the site of the fovea centralis was a cherry-red patch, not very dark, a little smaller than the disk, and with ill-defined outline."

It is well recognized that syphilis is not a factor in the disease; and hitherto no genuine case of amaurotic idiocy has been recorded in any but Jewish children. It has been asserted that the disease is restricted to Polish Jews, but this is not so; German and Polish Jews are likewise affected.

Sachs [13], in his recent paper on the disease, gives it as his opinion that the tendency to the disease is born unquestionably with the child, and that it is not acquired, nor due to a toxic cause. Afflicted children are "possessed of a nervous system so inadequate to the demands imposed upon it that its cells, after having performed their function for a few weeks or months, undergo complete disintegration."

More than one observer has recorded cases which in some degree resemble amaurotic idiocy, but which lack certain characteristic features. The family element may be absent; but it must be remembered that in but few such cases can we be sure that no more children would be born to the parents.

It has been stated above that the true disease is found only among Hebrews. Wandless [19] has recently reported, as atypical examples of amaurotic idiocy, three cases in a family known to be five-sixths Irish. One of the children was 14 years old when he died, and a second was

8 years old at the time of observation. The choroid and retina were atrophic, the latter showing pigmentation; the usual changes in the macula were not present. The autopsy showed complete optic atrophy. The retinal layers were hopelessly degenerated and no ganglion cells could be found. The ganglion cells throughout the whole nervous system were markedly degenerated, and degeneration was observed in the thymus, adrenal bodies and pituitary gland.

Parhon and Goldstein [9] record the first case observed in Roumania. The child was a Jew and was 14 months old.

Spielmeyer [17] describes a special form of the disease in which mental weakness, blindness, and a family character of the illness were present, but the former did not show itself till 6 years of age, and death did not occur until puberty.

Spiller [18] also refers to a patient whose illness was allied to amaurotic idiocy, and who lived until 8 years old.

Gordon [4] reports two cases of Russian Hebrew children, a brother and sister, in whom mental deficiency was noted in infancy, and blindness very early in life. Optic atrophy was present, and an irregular patch of absorption of choroidal pigment was observed in each eye, but there was no cherry-red spot at the fovea. He urges the opinion that anomalies in the structure and function of the ductless glands may be the real cause of the disease.

Kingdon and Russell [6], in 1897, published a paper dealing with "infantile cerebral degeneration with symmetrical changes at the macula." Five children in a family of seven were affected. In one of these cases an autopsy was made, when degeneration of the cortical pyramidal cells was found, with sclerosis of the pyramidal tracts; and a large amount of free fatty material was distributed throughout the sections. There was no evidence that these changes had occurred in other than normally developed tissues. The authors state that "so far as has been discovered the lesion is purely cortical, and it is just possible that the retinal changes are due primarily to a degeneration of the ganglion cells similar to that met with in the pyramidal cells of the cortex, and that the limited ophthalmoscopic appearance is partly due to a much greater abundance of those cells in the macula region."

Schuster [16], in a comprehensive survey of the subject, mentions five types of the disease, but he points out that, although their general similarity is remarkable, it is doubtful whether they can all be correctly included. Some stress is laid upon the fact that the disease is independent of any lesion of the blood-vessels. In the case which he reports the child died at the age of 15 months. The rods and cones were

normal in places, but swollen for the most part. In the foveal region the outer nuclear layer showed the following change—namely, the cells were placed in a convex layer as though increased in the direction of the vitreous, whilst the scleral side showed concave formation. The inner nuclear layer was much altered, many cells having perished. The outer molecular and Henle's layer were very much pronounced and less firm than usual. Schuster thinks that from the various changes seen œdema of the macula region was present. He says that no absolutely normal ganglion cells were present in the retina, and he summarizes the changes of individual cells as follows: Increase in volume; nucleus eccentric, dark and surrounded by dense protoplasm; knot-points of meshwork which fills cells thicker than normal; Nissl granules not preserved; gradual vacuolation. In some cells the diseased dendrites were clearly seen.

A few years ago Schaffer, of Budapest [15], contributed an interesting and well-illustrated article on this disease. He characterizes the minute pathology of amaurotic idiocy as a cell swelling. The details are best seen at the ampulla-shaped swellings on the dendrites; the individual fibrils are made to stand out, and their wave-like form is remarkable. Schaffer insists that it is the interfibrillary material which is first attacked, and that the cell degeneration follows. This view is supported by observers who consider that it is the interfibrillary substance or hyaloplasm of the cell and dendrites which carry the nervous impulse. Glia proliferation was well demonstrated. Bielschowsky's method showed that the optic nerve was normal, the inference being that the loss of vision was caused by a central cortical lesion.

From an examination of cells stained by Nissl's method, Schaffer concludes that the cell body is filled with two forms of network—namely, the nervous framework or inner neuro-reticulum, and a non-nervous spongioplasm (Cajal). The latter is more clear in pathological cells because in these the Nissl bodies have disappeared.

It was further observed that the structure of the cell nuclei was peculiar; the nucleus was seen to consist of threads, which possibly corresponded to chromatin, and which formed a network, which occurred in part only of the nucleus. This is not seen in normal nuclei, and Schaffer thinks it possible that disease of the cell causes a temporary greater activity of the nucleus. All parts of the cortex showed a remarkable lack of fibres. Schaffer concludes by expressing the opinion that children with amaurotic idiocy possess an abnormally exhaustible nerve-cell protoplasm, which, becoming paralyzed with the strain of the earliest functions, soon degenerates.

The characteristics of Mott's two autopsies [8] were: Absence of healthy cells in brain and cord; absence of Nissl granules in most of the Betz cells; glia proliferation; sclerosis of pyramidal tracts. No fibrils were seen coursing through the cells, as described by Gordon Holmes. In the case of the second patient (Case IA), Mott found acute inflammation of the liver and pancreas, which suggested a toxic cause for the illness. In the brain there was almost complete disappearance of tangential fibres, with marked diminution of the super-radial and inter-radial fibres. The radial fibres were abundant (Weigert-hæmotoxylin). The anterior and posterior cord roots showed fairly normal bundles of myelinated fibres, indicating that, although profound changes had occurred in the cytoplasm of the ganglion cells, the axons were still capable of function. This fact is important, taken in conjunction with the statement that it is the interfibrillary substance of the cell, and not its fibrillary conducting material, which suffers the primary, and so far invariable, change in the disease.

Mott, in 1907, thought it probable that every nerve-cell in the body was affected by the morbid process, and he concluded that "this extraordinary regressive metamorphosis is brought about by a conspiracy of morbid factors—namely, an inherent racial lack of specific neuronic energy and some general alteration in the chemical composition of the blood, either by the existence in it of a neurotoxin, or by the failure of some chemical substance to form in sufficient quantity, for the building up of the nucleo-proteid substance of the nervous system."

The most important observations which have been made on the disease in England in recent years have been embodied in papers by Mott in the *Archives of Neurology*, 1907 (*vide supra*), and by Poynton, Parsons and Gordon Holmes in *Brain*, 1906 [10]. The following conclusions were arrived at by the latter authors as the result of an elaborate microscopical examination of the nervous system:—

(1) That there is strong evidence that amaurotic family idiocy is a primary disease of the nervous elements, and that the neuroglia proliferation is secondary to this degeneration.

(2) That inasmuch as the nerve-cells are relatively more affected than the fibres, and as in certain tracts there may be no visible change in the fibres, the affection may be considered a primary cell disease.

(3) That the primary change is disease of the interfibrillary protoplasm, because this is very much more severely affected than are the neurofibrils. They also conclude that: (*a*) The disease is not due to arrested development, because there is no reason why, if this were the case, such an arrest should cause a progressive and invariably fatal

disease; and because, if it were so, the symptoms would probably be evident from birth. There is also little anatomical evidence of maldevelopment. "The most easily obtained evidence of the completed development of the central nervous system—namely, myelination of the fibres—proves that the final development of the different parts of the brain is completed at different periods in a fairly long space of time, and is not ended until a few months after birth. But the examination of these brains does not indicate greater abnormalities in the regions which develop late than in those where development is completed early in intra-uterine life—e.g., the visual cortex, which is myelinated very early, is quite as severely affected as the prefrontal region in which the myelinated fibres appear late. If, however, the disease dates from the earlier months of extra-uterine life, the development of fibres which myelinate late may be checked, owing to deficiency of trophic influence from the diseased cells." (*b*) The disease is not due to bacterial toxins, but to (*c*) some inherent biochemical property of the protoplasm of the cells, as the result of which it undergoes certain changes which result in its degeneration."

The authors further state that, on pathological grounds, the disease is one "sui generis," and must be separated from the class of diplegias. In this disease the nerve-cells are reduced in number, and those which remain are shrunken and atrophic. The myelinated fibres are those most greatly affected, and, unlike amaurotic family idiocy, the disease is often associated with gross defects or macroscopical changes in the brain.

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PART II.—By Dr. Mott.

Histological and Chemical Examination of the Nervous Structure.

Preface.

The histological and chemical investigations contained in this communication were carried out in the Pathological Laboratory of the London County Asylums, Claybury. A portion of the microscopic investigation was made by Dr. Carlyll under my direction, and I wish here to acknowledge my indebtedness to Dr. Fortuyn for his investigation of the cell lamination in the visual and auditory areas; to Dr. Edgar Schuster for three very admirable drawings, and to my assistant, Mr. Sydney Mann, for his chemical investigation, the results of which form an appendix.—F. W. Mott.

Introduction.

I described two cases of this disease very fully in vol. iii, *Archives of Neurology*. I mentioned there my reasons for terming the disease amaurotic dementia rather than amaurotic idiocy. I pointed out that the brains were of normal size or even larger than normal average; moreover, the convolutional pattern was in no respect like that of an idiot's or imbecile's brain; in these two cases the Sylvian fissure did not slope obliquely upwards and backwards as in the simian brain, and the superficial surface of grey matter, owing to the complexity of the convolutions, was by no means deficient in extent; neither did the microscopic examination of the cortex cerebri indicate a deficiency in numbers of the cortical cells. Moreover, I showed that the same characteristic change which is known to affect the cerebro-spinal ganglion cells also affected the sympathetic.

I have since had the opportunity of examining four such brains of children dying of this disease, three of which were from Cases I, III and VII. In all these cases the brains were of normal average weight, and the convolutional pattern complex, and in no way denoting either imbecility or idiocy. Again, I have had the opportunity of examining the central nervous system in all these cases, and I do not find a deficiency of numbers of the cortical cells. Moreover, the sympathetic ganglion cells I found showing the same change, only not

so advanced as the cerebrospinal ganglion cells. It may, therefore, be concluded that the disease is an affection of the whole of the neurones of the body. It cannot be present long before birth or the convolutional pattern would not develop to its perfect form. We have to ask ourselves, therefore, what is the cause of this extraordinary disease, in which the microscopic morphological changes in the nervous system, and the clinical phenomena are so characteristic as to be unmistakeable for any other disease? Is it an acquired disease? If so, what conditions of life should limit this disease to the Jewish race. So far, I have been unable to associate it with any condition of food or environment; it appears to occur in both breast-fed and artificially-fed children, and I am inclined to agree with Sachs that there is little evidence to show that conditions of food or environment can account for the disease. Since it affects only the offspring of Jewish parents, and frequently several of the offspring of the same parents suffer with this disease and die of it, it follows that racial and family heredity do play a part, and probably are solely responsible for its occurrence.

Morphological and Chemical Investigations in Relation to the Pathogenesis.

The evidence I have adduced shows that all the nervous units are present at birth, but from some cause or other their specific vital energy is so deficient that they are unable to maintain physiological equilibrium; they are unable to store any reserve of the Nissl substance which many authorities regard as the material basis of nervous energy; in consequence of this, and probably also from the swelling of the cell, the conductile mechanism itself (neurofibrils) undergoes destruction, with morphological and bio-chemical changes in the neurones. As the neurones degenerate and die the neuroglial cells proportionally proliferate and increase in size, thus altering the consistency and feel of the brain itself, which has a tough, leathery character. Do the neurones die because of an inborn deficiency of specific vital energy, or do they die because the ambient medium contains some toxic substance or lysin which destroys them, or is it because the ambient medium is lacking in some substance necessary for the development and maturation of the neurones? If it were a toxin or lysin we should rather expect it would act equally on all the cells of the body, and certainly all the nerve-cells, which is not the case. It might be a deficiency in the blood of some substance, for we know that cretinism is due to an absence of the

thyroid gland; but cretinism is a condition of obvious defective brain development—in fact, we have an idiot's brain. The thyroid is not affected in Tay-Sachs disease, nor can I find any gland which is affected; and I have examined all the tissues of the body in several cases. We now come to the only other cause—viz., an inborn lack of specific vital energy of the nerve-cells, due to a racial inherited failure of the germinal determinants of the nervous system.

The neurones are perpetual elements, they are all present at birth with all their innate potentialities to respond to stimuli from without; this leads to their acquiring connexions and associations with one another; in no part of the body, excepting the reproductive organs in adolescence, do such important synthetic chemical changes take place as in the central nervous system of the human being in infancy. The Nissl substance has to be accumulated in the nerve-cells, especially in those of later phylogenetic and ontogenetic development; the myelin has to be deposited around the axial fibres of the neurones, particularly in the brain cortex, where there is scarcely any present at birth. How is this accomplished? Although stimulus from without by all the sensory avenues plays some part in accelerating this synthetic process, nevertheless every neurone has a specific autonomic inherited energy apart from stimulus. The experiments of Ross Harrison demonstrate the truth of this fact. The principles of heredity tell us that this autonomic specific energy resides in the nucleus, which is the soul of the neurone; and the experiments of Loeb upon parthenogenesis in Sea Urchin eggs show that the nucleus possesses an auto-katalytic ferment, which in the process of segmentation of the egg-cell in reproduction is capable of decomposing the lipoids of the cytoplasm and recomposing from the products a more highly phosphorized substance, nuclein.

The experiments of Verworn and others tend to show that the Nissl substance is a store of reserve neural energy, and it is contained in the meshwork of the conductile neurofibrillary substance; the observations of Macallum showed that it is a nucleo-protein containing phosphorus, and it is not unreasonable to suppose that the nucleus of the neurone produces a ferment substance which, passing into the cytoplasm, elaborates the Nissl substance out of a phosphorized lipoid obtained from the ambient medium; this basophil chromophilous material contained in the interfibrillary meshwork forming a pattern according to the arrangements of the fibrils. Verworn and his pupils' experiments indicate that this substance unites with oxygen and forms a store of neural energy. Marinesco terms it kinetoplasm.

Now, if we study the microscopic morphological characters of this disease we shall note a very remarkable and characteristic disappearance of the Nissl granules, so far as I am aware, not observable in any experimental conditions, such as ligature of blood-vessels, hyperpyrexia, or toxic conditions in mammals. Nor have I seen such change in any human pathological condition. Generally, when the cell is swollen the nucleus becomes eccentric and the Nissl granules are only found at the periphery of the cell; the chromatolysis is perinuclear, just the converse of what is found in this disease. In alcoholic and lead neuritis the anterior horn cells and the Betz cells of the cortex show perinuclear chromatolysis, which is doubtless due to reaction of injury to the axon combined with toxic conditions of the blood.

In Tay-Sachs disease, as is well known, the Nissl substance disappears from without inwards towards the nucleus, and as the Nissl substance vanishes so the cell swells up as if a process of hydrolysis had taken place. In the later stages no Nissl substance can be seen upon the dendrons, which are also swollen irregularly; no Nissl substance can be seen in the greater part of the cell body, which has undergone a bladder-like distension and often curiously and characteristically distorted into an hour-glass shape. The swelling and distortion of the cell is generally proportional to the disappearance of the Nissl substance, and finally there is only a halo of deeply stained basophil substance around the nucleus, which may now be displaced from the centre of the cell; in the case of the pyramidal cells of the cortex it nearly always takes up a position at the base of the apical dendron (*vide* fig. 13 (1)). If the sections are stained with toluidin blue or polychrome blue it will be found that the bladder-like swollen cells show a fine intracellular network which stains at the nodal points (figs. 13 (4) (5)); the network stains owing to a film of incrustation of basophil chromophilous substance. Later, when the change is more intense, the network is incomplete and unstainable areas are seen. I have, so far, only dealt with the cells stained by basic aniline dyes, but we shall not have a true picture of this disease unless many methods of staining are adopted—methods which are applicable to the demonstration of particular structures.

I shall now advance proofs that the process of decay and death of the neurones is characterized by a fatty degenerative change with destruction of the intracellular neurofibrils; there are also changes occurring in the staining reaction of the nucleus, and eventually the nucleus itself is destroyed, although that is a comparatively infrequent event.

CELLULAR CHANGES.

The nuclear membrane is sometimes stained with basophil dyes deeply; also the nucleolar and intranuclear network. Generally in cells which show a marked degree of swelling, the nucleo-plasm also stains with the basic dye. In the normal cell the nucleo-plasm is unstained by basic dyes. This microchemical basophil reaction suggests a change in the normal biochemical function of the nucleus. Are these cell changes due to a failure in the ambient medium of the necessary materials which may be required by the nuclear ferment to form the nucleo-protein Nissl substance, or is it some progressive failure of the nucleus in its reaction on the cytoplasm, causing the cell to swell up and eventually break up and destroy the intracellular network? The dendrons also show characteristic swellings (*vide* fig. 13 (8) (9), and fig. 15). Although all the nerve-cells of the central nervous system show the fatty change in some degree, including the ganglion cells of the retina, which, as we know, are developed by a bud from the forebrain, yet the neurones are not equally affected in the whole nervous system, nor even in sections of the same part; therefore, specific cell energy does play a part, whichever view is taken, regarding the pathogenesis. The chemical analysis of the brain as compared with a normal child's brain of the same age shows a deficiency in organic phosphorus and sulphur, and an increase of water-soluble extractives, containing phosphorus and sulphur. Consequently we cannot suppose that there is an increase of lipoids in the cells, due to accumulation; but it rather shows that the nucleus provides a splitting ferment, whereby the cell-plasm is decomposed and broken up, but the nuclear activity does not complete the vital process by a synthetic action; thus there may be a chemical decomposition on the way to a fatty acid, e.g., choline, glycerophosphoric acid and stearic acid, and no recomposition. A fatty acid or soap, or some lipoid, which takes the Scharlach stain in various degrees of intensity, may account for this reaction. The cells are also stained by the Marchi-Pal and Heidenhain methods in varying degrees of intensity; in all cases taking the form of very minute particles, which is additional evidence of its fatty degeneration. In the cortex of the cerebrum and in the cerebellum, where the degeneration is most intense, an immense number of granule cells (Körnchenzellen) are seen; these contain larger ruby red granules, and are seen scattered throughout the whole of the cortical grey matter of both the cerebrum and the cerebellum. At first I

thought these were ganglion cells, but when Scharlach-stained specimens are counter-stained with methyl violet, with methyl blue, or logwood, it is then seen that these cells have a nucleus in the middle, and that several together lie on a ganglion cell, and almost, or completely, obscure it; sometimes two of these granule cells, joined together, occupy the position of a degenerated ganglion cell, and take on the characteristic hour-glass appearance. It may generally be said that the nerve-cells very seldom indeed show any coarse granules. It looks as if the neuroglia cells possessed a phagocytic function, as was first pointed out by Bevan Lewis, and I have seen in both silver preparations and preparations stained by other methods (photomicrograph 5) appearances suggesting phagocytic activity of the neuroglia cells.

Two of the three brains examined showed numbers of granule cells in the white matter as well as the grey, this showing that these cannot therefore be ganglion cells which have undergone this degeneration. Numbers of cells filled with deep red stained fat granules are also to be seen in the perivascular lymph sheaths, as if the endothelial cells or cells of the adventitia had taken up the fatty matter. Curiously enough, not much change was found in the cerebrospinal fluid withdrawn during life by lumbar puncture.

All the facts show that in this disease there is a fatty degeneration of the cytoplasm of the neurones, which I find Alzheimer describes in a recent publication. The satellite cells found in the perineuronal spaces, or neuroglia cells, show a fatty change, which is probably of the nature of an infiltration; that is to say, these cells have devoured the fat produced by the degeneration of the neurones; the fatty contents of these cells indicate a further process of change, judging from the deeper coloration by the Scharlach dye, and the larger size of the globules (*vide* Plate I). The appearance of the nerve-cells of the cortex makes it possible that the late stages of hydrolysis convert the cytoplasm into a thick emulsion, giving the cell that peculiar appearance which is not unlike that of the cortical cells of the suprarenal body, which we know contains a phosphorized fatty substance that stains deeply with Scharlach R. Moreover, I have noticed that when there is a considerable amount of glia fibrillation of the superficial layers of the cortex, and the microscopic examination of sections of the cortex shows a marked condition of fatty change in the cells (*vide* photomicrograph 8), that the brain substance is semifluid, like cream, so that the tough, leathery, fibrillated superficial layer of the cortex can be peeled off from the subjacent semifluid, creamy grey matter.

DETAILED DESCRIPTION OF FIGURES AND PHOTOMICROGRAPHS.

I will now describe, with the aid of the accompanying figures and photomicrographs, the cell changes which occur when sections have been stained by particular methods.

Fig. 13, a number of cells showing morphological changes.

(1) A large pyramidal cell of the cortex from a Scharlach-stained section counterstained with hæmatoxylin; the whole cytoplasm is stained an orange-pink; it presents a fine granular appearance. The cell is swollen, the nucleus is pushed up towards the base of the apical dendron, and from the base of the cell there is an oval, bladder-like swelling. (Magnification 500.)

(2) A similar pyramidal cell stained with Weigert-Pal; the cytoplasm is filled with minute blue-stained globules. The cortex stained by Marchi method would show similar globules stained blackish-grey. Again, Heidenhain's hæmatoxylin stains these fine globules blue. These fine granules thus stained may be protoplasmic particles covered with a film of fat or soap; they are the same as the fine granules seen in (1). (Magnification 500.)

(3) A cell stained by Scharlach R or Sudan III, showing much larger granules stained deep red. Most of these, and they are very abundant in the cortex, are Alzheimer's Körnchenzellen, and are either neuroglia cells or satellite cells filled with fatty droplets. It is very difficult to say whether any of the ganglion cells ever present such an appearance. (Magnification 500.)

(4) A large cortical pyramidal cell stained with toluidin blue as recommended by Schaffer, to demonstrate the intracellular network; it also shows the swelling and characteristic almost hour-glass distortion; the Nissl substance has almost entirely disappeared; there is still a little incrustation of the nodal points of the intracellular network around the nucleus. (Magnification 500.)

(5) A large spinal anterior horn cell; the same description applies as above in 4. (Magnification 500.)

(6, 7, 8, 9) Various pyramidal cells of the cortex stained by Cajal's neurofibril method. Sections were also stained by Bielschowsky's method, but the results as regards the points to be described are the same. (6) shows the basal neurofibril process split, the fibrils passing down each side of a pale substance which appears to consist of globules or round particles; the nucleus is connected with fibres coming in from the apical dendron. In (7) an appearance which is very rarely seen is

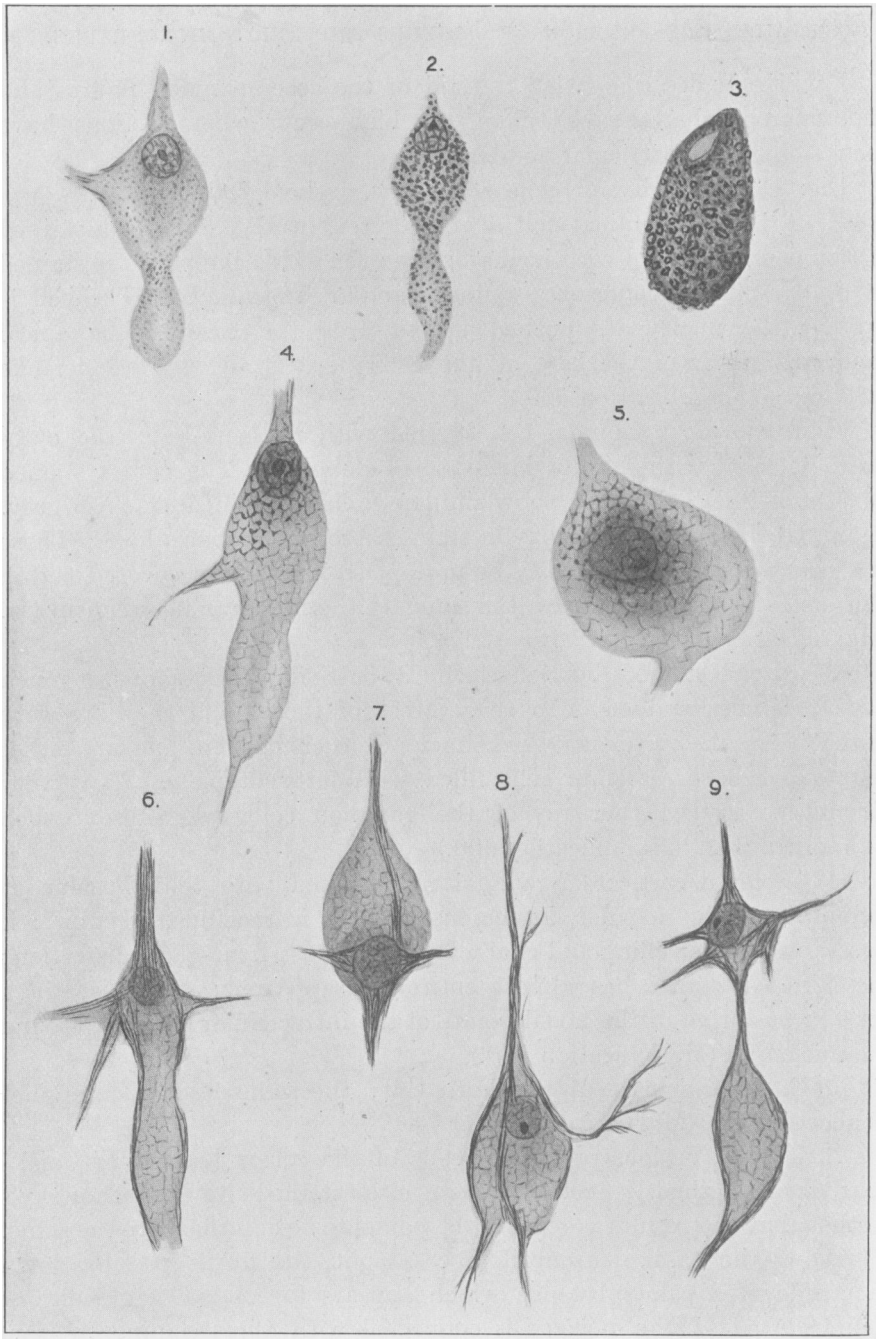
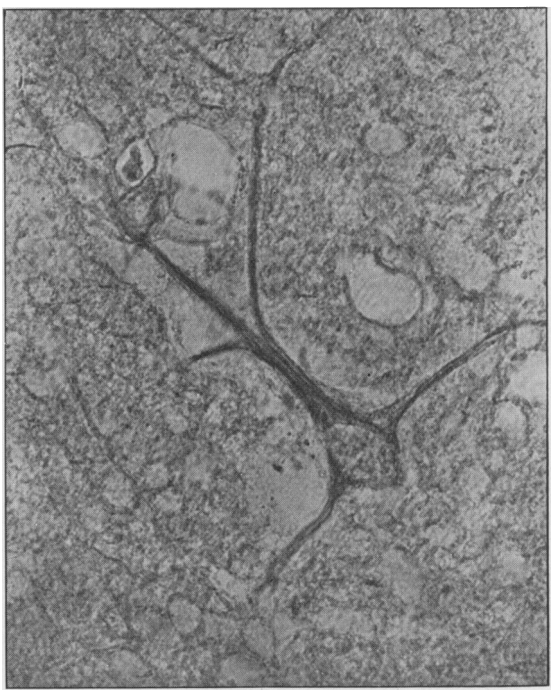


FIG. 13.

shown; here the nucleus is apparently held in position by intact neurofibrils passing across the cell from one lateral dendron to the other. (8) shows an appearance not infrequently seen of the fibrils of the apical dendron passing along the periphery of the cell to other processes. (9) shows a large ovoid swelling on one of the processes of a ganglion cell as if the hydrolytic process had commenced in the process instead of the body of the cell. (Magnification 400.)

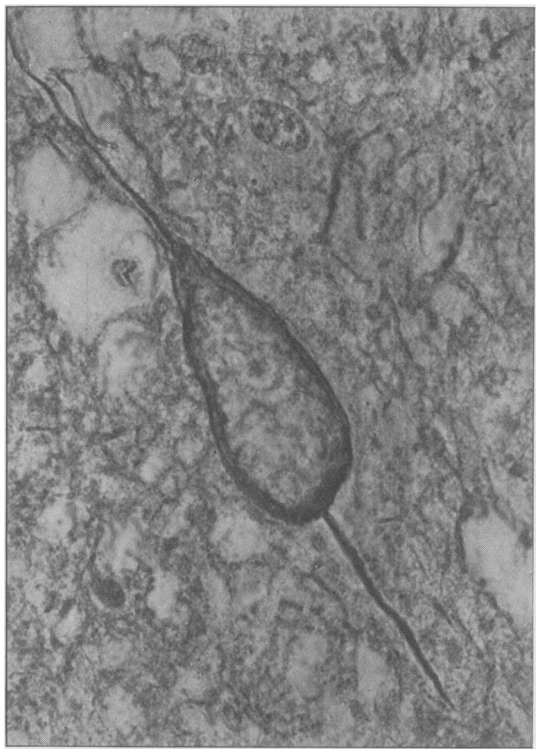
Photomicrograph 1.—A nearly normal cortical pyramidal cell showing abundant neurofibrils in the processes; this was the only one seen in a section showing hundreds of cells in a state of degenerative decay. (Magnification 1,080.)



PHOTOMICROGRAPH 1.

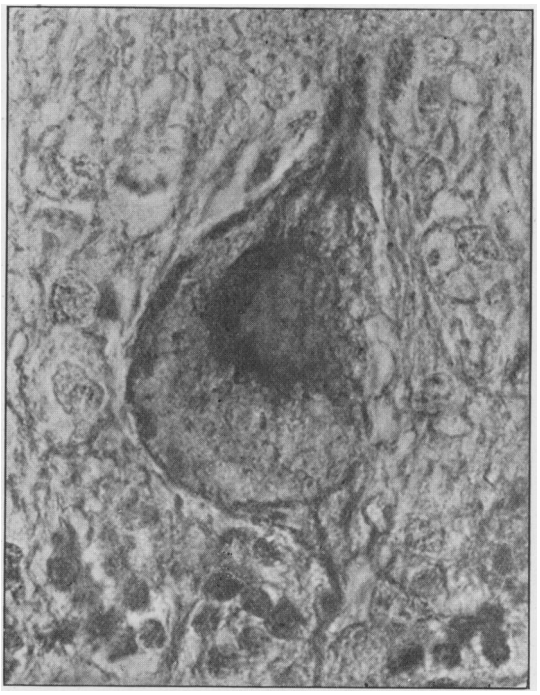
Photomicrograph 2.—A pyramidal cell in which the only fibrils are seen at the periphery and in the two processes. The fibrils seem to be continuous between the apical dendrons and the axon. The whole central portion of the cytoplasm has a coagulated structureless appearance. (Magnification 1,180.)

Photomicrograph 3.—A cell of Purkinje stained by the neurofibril method. The fibrils can be seen passing from the apical dendron to the nucleus and around the periphery of the cell continuous with the fibrils of what appears to be the axon, arising from the lower portion of the distorted, flask-shaped cell. It will be observed that all around the nucleus there is a complete absence of fibrils. I attribute this to the disappearance of the basket-like terminal arborization of the stellate cells, which a subsequent illustration will show are degenerated earlier than the Purkinje cells. (Magnification 1,260.)

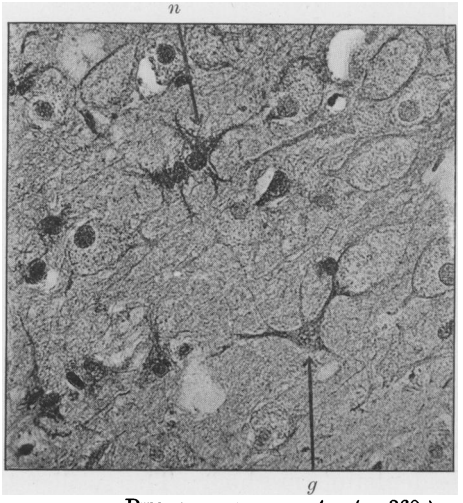


PHOTOMICROGRAPH 2.

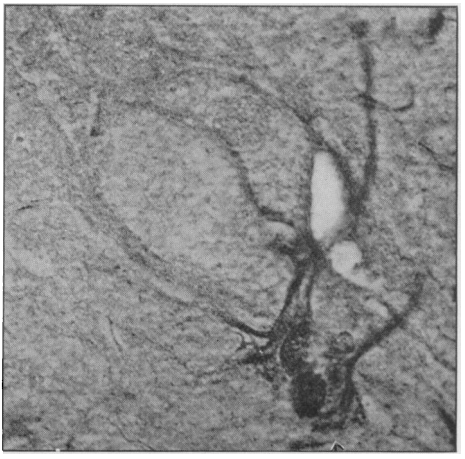
Photomicrograph 4.—Cortex stained by neurofibril method. Numbers of bladder-like cells are seen with a fine granular central portion and externally surrounded by dark-stained fibrils; *g* shows a ganglion cell which apparently is intact as regards its neurofibrils except that one process appears to be surrounding a degenerated cell. It will be observed that this nerve-cell differs markedly from the black-stained



PHOTOMICROGRAPH 3.



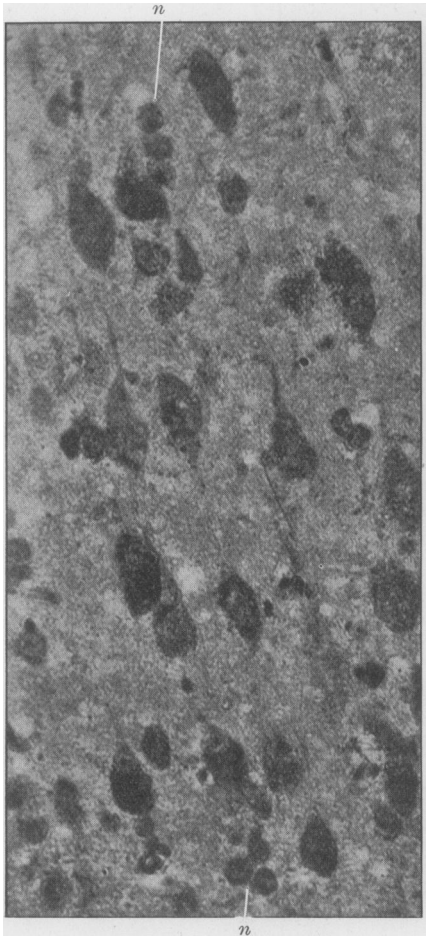
PHOTOMICROGRAPH 4. (× 360.)



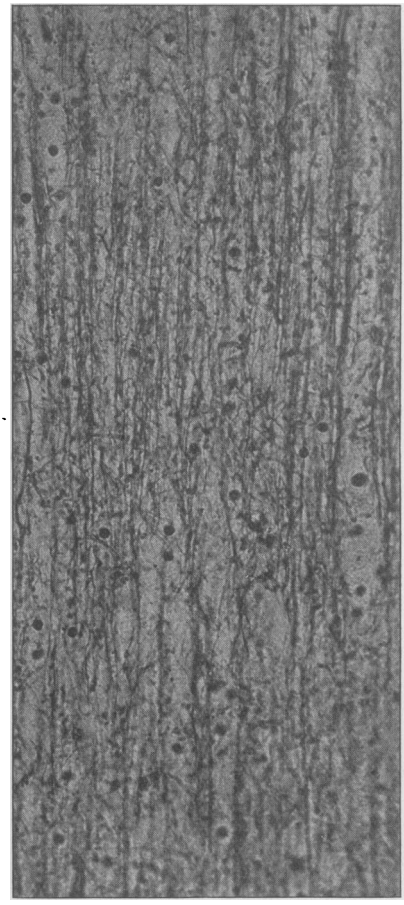
PHOTOMICROGRAPH 5. (× 810.)

neuroglia cells *n*, of which there are great numbers undergoing proliferation. (Magnification 360.)

Photomicrograph 5.—A large neuroglia cell, showing two nuclei and large stout processes, apparently stuck on to and grasping with its processes a large degenerated ganglion cell, but some of the fibrils which seem to come from the glia cell can, by close observation, be seen



PHOTOMICROGRAPH 6.

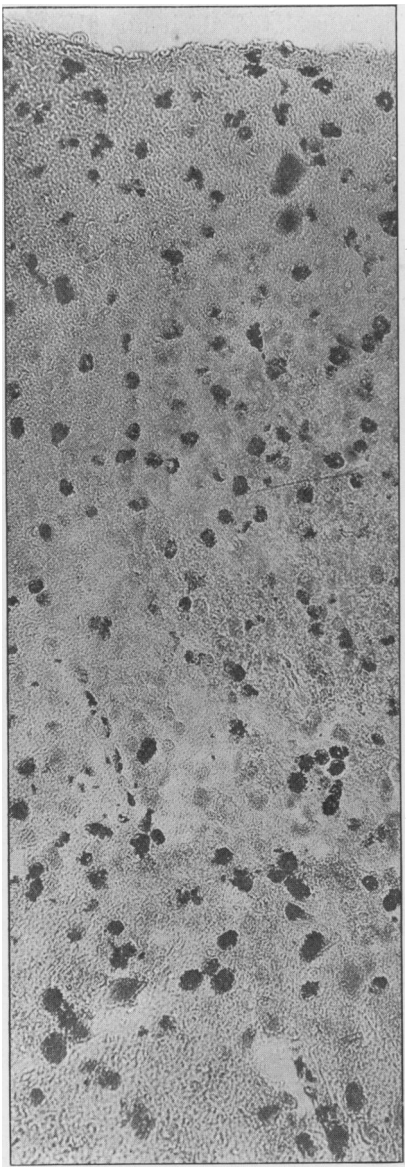


PHOTOMICROGRAPH 7.

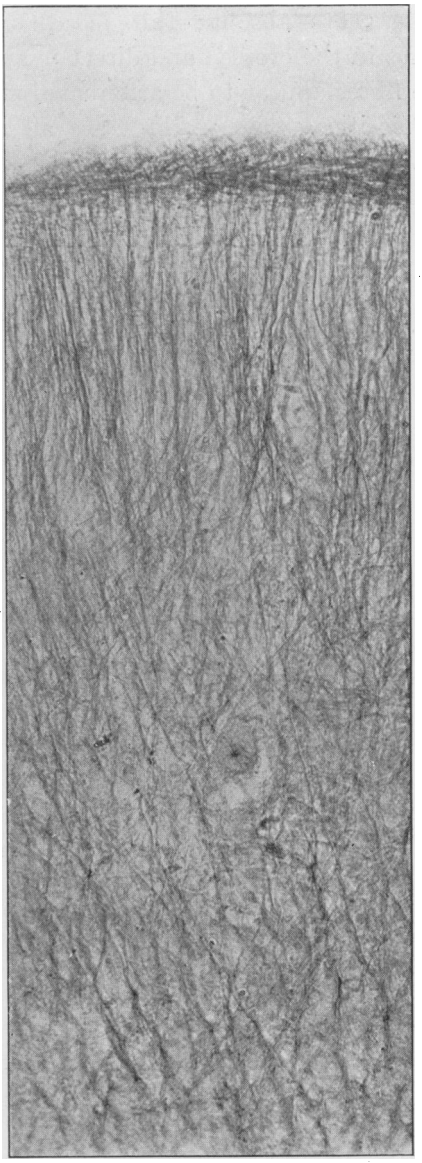
to be the undestroyed peripheral neurofibrils of the ganglion cell. (Magnification 810.)

Photomicrograph 6.—Cortex stained by Weigert (neuroglia method), subsequently by iron hæmatoxylin (Heidenhain's method). The swollen, distorted, bladder-shaped pyramidal cells are stained purple owing to

the fine fatty globules. The nucleus is not stained deeply and it can be seen pushed up to the apical dendron. At the bottom of the picture and at the top can be seen three cells in groups *n*, round in form; these are Körnchenzellen, or granule cells, and with Scharlach or acid fuchsin are stained deep red. In the middle of the picture several can



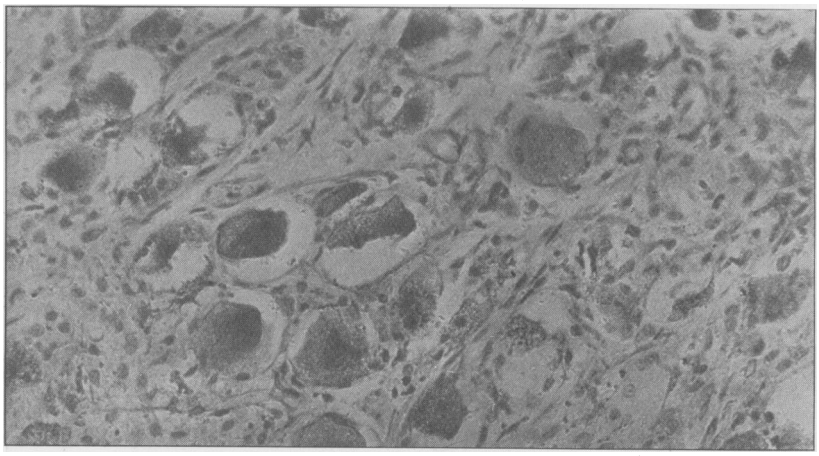
PHOTOMICROGRAPH 8.



PHOTOMICROGRAPH 9.

be seen sticking on the degenerated ganglion cells. No axis cylinder processes can be seen. (Magnification 380.)

Photomicrograph 7.—A Weigert-Pal-stained section of the subcortical white matter of the ascending frontal convolution; it will be observed that there are no coarse fibres characteristic of this cortical area present. This indicates that the large coarse fibres which form the pyramidal system are absent; this fact may be correlated with an absence of fibres in the crossed and direct pyramidal tracts of the spinal cord. All the fibres appear to be attenuated and most of them show degenerative varicosities. These fibres are all radial fibres and it will be observed that there is a complete absence of inter-radial association fibres. (Magnification 330.)



PHOTOMICROGRAPH 10.

Photomicrograph 8.—Section of the cortex stained by Scharlach R. The deeply stained cells are Körnchenzellen, the fainter stained cells with fine granules are the ganglion cells (*vide* also Plate I). (Magnification 180.)

Photomicrograph 9.—Section of the cerebellum stained by Ranke's Victoria blue method. Enormous increase of Bergmann's neuroglia fibrils is seen and a dense felting of the surface. (Magnification 450.)

Photomicrograph 10.—Section of the sympathetic (inferior cervical) ganglion showing peripheral chromatolysis of many of the cells; the change in the sympathetic ganglion is not so advanced in this case as in others that I have examined.

Fig. 14.—Section of cortex stained by Weigert-Pal method showing the terminal arborization of degenerated fibrils around cells, the bodies

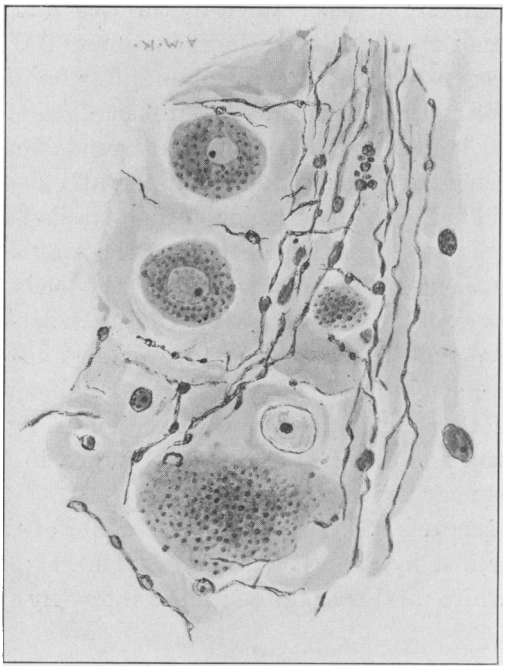


FIG. 14.

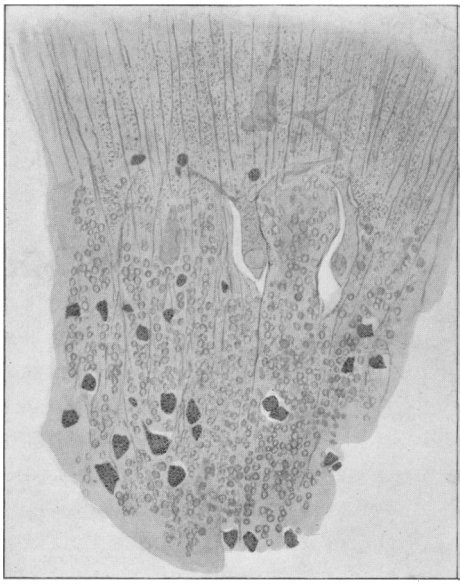


FIG. 15.

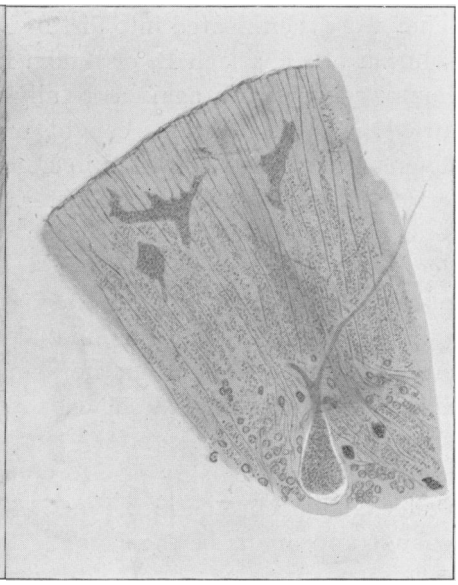


FIG. 16.

of which show minute globules stained by the dye in the same manner as the degenerated nerve fibrils. (Magnification 800.)

Fig. 15.—Frozen section of cerebellum, after hardening in formalin a few days, stained with Scharlach. A number of deeply stained smaller cells are seen amidst the granules which are unstained, many of them doubtless are Körnchenzellen; some are apparently degenerated stellate cells—viz., the cells, the axon of which form a basket-work around the Purkinje cells; the degeneration of these cells would account for the absence of fibrils seen in the greater part of the body of the Purkinje cells (photomicrograph 3). The Purkinje cells are visible because stained a pinkish orange, and the dendrons are swollen and similarly stained owing to fine granules of fatty substances. (Magnification 200.)

Fig. 16.—Another portion of the same section as fig. 15, but showing more distinctly the fine particles of fatty substance in fragments of the swollen dendrons near the surface.

As a control sections of brain of a normal child of the same age were prepared and stained by Scharlach R and Sudan III; the cells are not visible, but the white matter is stained more intensely a deep orange red.

Examination of the Retina.

Portions of the retina were removed from one eye, Case VII (*vide* p. 165), and preserved for a few days in 10 per cent. formol solution. They were then floated into distilled water, and transferred to an alcoholic solution of Scharlach R, or Sudan III, in which they were left for some hours. They were again carefully floated into weak alcohol to wash away the excess of stain, caught on a cover-glass with the ganglionic layer upwards, and mounted in Farrant's solution.

Fig. 17.—Drawing by Schuster. (Magnification 240.)

The ganglion cells in the retina can be distinctly seen, owing to their deeper staining. They appear to be much more numerous in some places than others. They vary considerably in size, as the drawing (fig. 17) shows. As this method shows the whole cell it must be either assumed that as in the spinal ganglion there are cells of varying size in the retina or that the cells differ in size owing to the pathological change. Against this is the fact they are all uniformly stained a deep orange colour, in many places on an unstained background. Moreover, under an apochromatic 2 mm. 140, 4 comp. ocular, the pathological change appears to be the same. I am therefore led to believe that the difference in size is due to different-sized ganglion cells in the retina, a fact which sections would not show.

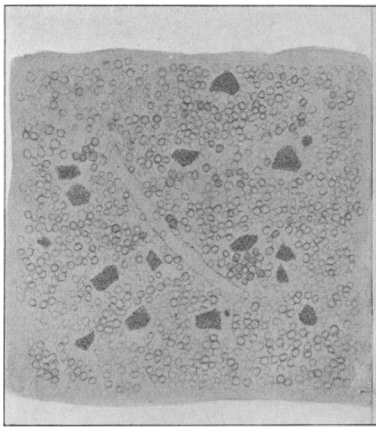


FIG. 17.

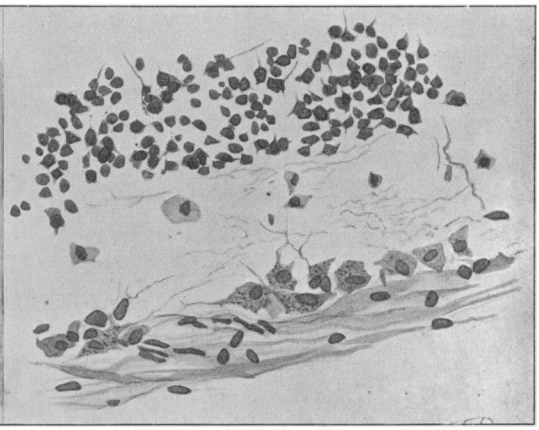


FIG. 18.

Fig. 18.—Stratum opticum. Ganglionic layer, inner molecular and inner layer of granules. (Magnification 450. Schuster.)

The other eye, after hardening in 10 per cent. formol, was embedded in celloidin, and sections through the whole eye were cut and stained by polychrome blue, Nissl, Giemsa, and Van Gieson methods. The only definite observable changes were in the ganglion layer. The cells appear abnormal in shape, the processes are either indistinctly seen or obscure. The cells lie in confused clumps, in places appearing as if joined together. The nuclei and nucleoli are well stained, but the cytoplasm is poorly stained, and appears to consist of a fine intracellular network faintly incrusted with basophil substance. No Nissl granules are seen. Here and there ganglion cells can be seen with a swollen process.

The observations of Dr. Fortuyn show that the whole cortex is similarly affected.

DESCRIPTION OF THE COLOURED PLATES.

The coloured Plates I and II are reproductions of drawings by Miss Kelley to show the appearances presented by Scharlach-stained specimens. It will be observed that the ganglion cells, wherever they are taken from, are stained a reddish-orange or orange colour. The granule cells are stained a deeper ruby-red. I may add that I have employed some of the methods of staining recommended by Lorrain Smith,[1] but I have not found that they yielded such good differentiating results as the Scharlach and Sudan III, or the fuchsin method of Alzheimer.

[1] Since this paper was completed I have received an important communication explaining the action of these various dyes on fats and lipoids: J. Lorrain Smith and W. Mair, "Fats and Lipoids in relation to Methods of Staining," *Skand. Arch. f. Physiol.*, Leipz., 1911, xxv, p. 247.

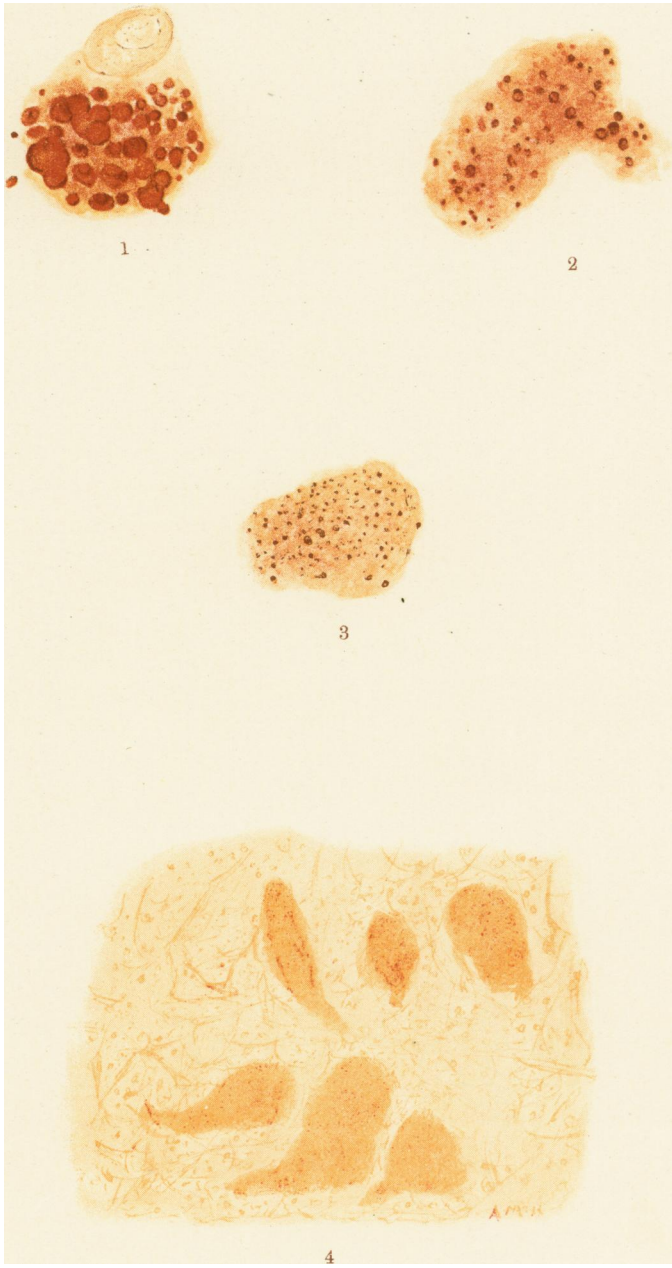
Explanation of Plate I.

Fig. 1 shows a cortical pyramidal cell swollen up, and filled with large red-stained fat globules of uneven size, and some coalescing. At the upper part of the cell is a pale unstained portion, which is apparently the nucleus. I found only very rarely ganglion cells showing this appearance. The vast majority of cells with red-stained large globules were the so-called granule cells (Körnchenzellen).

Fig. 2.—This is a distorted pyramidal cell, in which there are scattered small red globules. These, again, are rarely met with, and, as I have previously explained, many cells look like ganglion cells when only stained with the Scharlach, but which when counterstained by logwood or methyl violet prove to be one or several granule cells lying on the decayed ganglion cell, and I would not deny the possibility of this being the case in respect to both this (fig. 2) and that of fig. 1.

Fig. 3.—This is a ganglion cell in an advanced stage of fatty degeneration. The whole cytoplasm is permeated with fine globules of fat. (Magnification 600.)

Fig. 4.—A group of small cells of anterior cornu of spinal cord, stained by Scharlach. The cells are stained a pinkish-orange colour. One or two show a very fine granulation appearance. (Magnification 600.)



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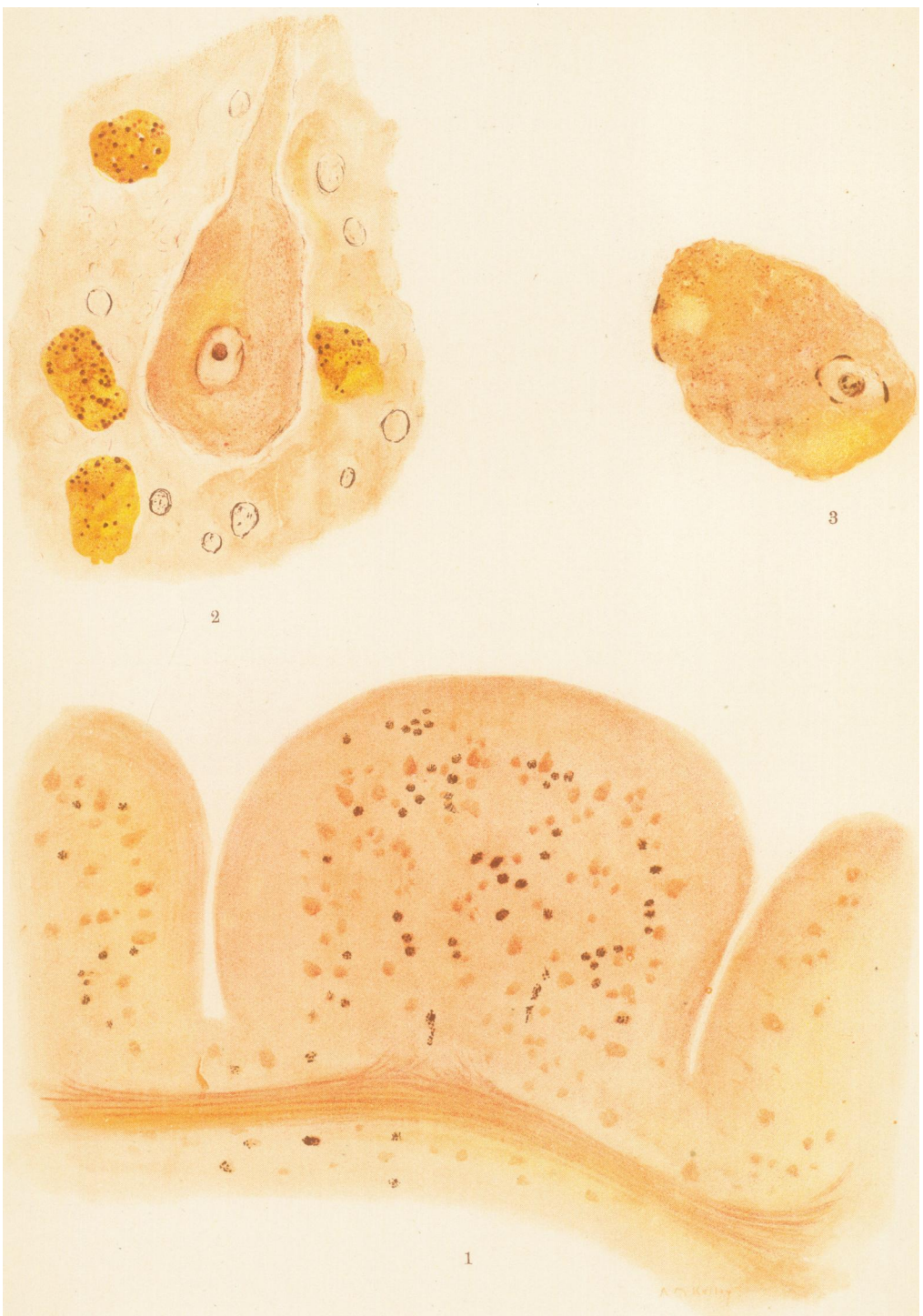
CARLYLL & MOTT: Seven Cases of Tay-Sachs Disease. Plate I.



CARLYLL & MOTT: Seven Cases of Tay-Sachs Disease. Plate II.

Explanation of Plate II.

Fig 1.—Section of cerebellum stained by Scharlach R. The cells of Purkinje are seen stained a light orange-red; also a number of much smaller cells are similarly stained. But besides these paler-stained cells, which are degenerated ganglion cells (stellate cells, second type of Golgi), there are scattered about a number of deep ruby-red cells arranged in groups and sometimes in rows. These are granulation cells—amœboid neuroglia cells filled with fat globules. This particular preparation from Case VII does not show any of these granule cells in the white matter; but in the other two cases which I have examined, numbers of these deeply stained granulation cells (Körnchenzellen) exist in the white matter; especially are they found in numbers in the perivascular sheaths. The small granules (nerve-cells) which form such a prominent histological feature of the cerebellum did not take the Scharlach stain. (Magnification 50.)

Fig. 2.—A Purkinje cell in an early stage of degeneration. It is covered all over with very fine pinkish-orange granules. In the immediate neighbourhood are four cells containing coarse red globules. I believe they are ganglion cells, but they may be granulation cells (Körnchenzellen) in an early stage of fatty change.

Fig. 3.—A Purkinje cell showing a rather more advanced stage of fatty change; it is more deeply stained red. (Magnification 600.)

It will be observed that the ganglion cells vary in depth of coloration by the Scharlach dye, and the deeper the colour the more obvious do the particles of fatty substance become. There is also a parallelism between the distortion in shape of the ganglion cell and the evidences of the fatty change. The fact that all the ganglion cells, with the exception of the granules, are degenerated in the cerebellum may account for the apparent absence of the basket of fibrils around the base of the cells of Purkinje; this absence of fibrils is shown in photomicrograph 3. If sections are placed first in alcohol, then in ether for a short time, the cells no longer stain, all the fat having been dissolved out.

Dr. Carlyll, in his historical summary, has given a résumé of previous observations on the morphology of this disease, but it is necessary for me to refer to some important observations by Alzheimer concerning the fatty change in ganglion cells in this disease, and in the amaurotic idiocy described by Spielmeyer and Vogt. These observations I had no knowledge of when I wrote this paper, but I have since found a description very similar to the above in Alzheimer's [1] valuable work, which he kindly sent me. He also gives a number of valuable methods of staining which I shall adopt in the study of a case that has recently died, under the care of Dr. Hume, of Newcastle, who has forwarded me the brain and the eye for examination. This will form the subject of a joint paper on the histology by the most recent methods.

Conclusions.

(1) Reasons are given why the term "idiocy" should be abandoned; it will be better to adopt the name "Tay-Sachs disease" until the pathogenesis is known.

(2) Reasons are stated why it is probably a failure in the germinal determinants of the nervous system peculiar to the Jewish race.

(3) The morphological and chemical investigations in relation to the pathogenesis are discussed, also the hypothesis is put forward that it may be due to a failure in the nuclear material of the neurones to build up the nucleo-protein Nissl substance out of lipoid substances contained in the cytoplasm, which first have to be decomposed by a nuclear ferment. The autokatalytic ferment action of the nuclear

[1] "Beiträge zur Kenntnis der pathologischen Neuroglia und ihrer Beziehungen zu den Abbauvorgängen im Nervengewebe." Nissl und Alzheimer, "Histologische und Histopathologische Arbeiten über die Grosshirnrinde," Jena, 1910, iii, pp. 401-554.

material of the fertilized ovum described by Loeb is considered as affording a somewhat analogous chemical process.

(4) Evidence to show that there is a progressive failure of Nissl substance proceeding from without inwards towards the nucleus and a corresponding accumulation of a fatty substance of the nature of a lipoid, which, accompanied by a process of hydrolysis, would cause a swelling of the cell and destruction of the intracellular neurofibrillary network.

(5) The chemical analysis does not throw much light upon the question; the diminution of the lipoid forms of phosphorus and sulphur is probably due to the diminution of myelin, owing to failure of development of the myelinated fibres. The corresponding increase of extractive forms of phosphorus and sulphur may be possibly due to a breaking down of the more complex to simpler forms of lipoids.

(6) The morphological changes are quite characteristic of the disease. All the ganglion cells stain with Scharlach in varying degrees of intensity, more or less intense in proportion to the degree of swelling and obvious morphological change; they also stain with Marchi, Weigert-Pal, Heidenhain—in fact, all the methods which stain the myelin sheath or fat. They do not, however, stain satisfactorily by Marchi, like degenerated myelin does when the process of decomposition has been complete to choline, glycerophosphoric and oleic acid. Consequently it is more correct to say that the cytoplasm *may be* on *the way* to this complete decomposition.

(7) Whereas the ganglion cells very rarely show *coarse* ruby-red globules of stained fatty substances, there are, especially in advanced cases, immense numbers of cells containing these coarse globules, and forming what Alzheimer terms Körnchenzellen; they are neuroglia cells which have taken up the fat from the dead and decayed ganglion cells, to which they may be seen sticking sometimes in little, closely aggregated groups indicative of active proliferation. It is probable that they have the power of decomposing this lipoid of the dead ganglion cells and possibly of recomposing nuclear substance necessary for their proliferation out of it.

(8) Other methods of staining—e.g., toluidin blue, Cajal silver, or Bielschowsky—show that the intracellular fibrils are ruptured and destroyed by the swelling leaving only the peripheral neurofibrils, which can be followed from the dendrons in their course around the swollen cell to other dendrons or to the axon. In the cortex, the fibrils of the apical dendrons are seen proceeding to the nucleus, which is usually

forced up into the apex of the pyramid. It is possible that the cytoplasm is of the nature of a thick emulsion, each particle consisting of a plasm covered with a film of fat or soap.

(9) The cells of the retina, when this structure is stained with Scharlach, show a similar change to the nerve-cells of the central nervous system; the cells are of varied size, apparently.

(10) In two of the three brains examined there was an accumulation of granulation cells (Körnchenzellen) along the course of the blood-vessels, also endothelial and connective tissue cells of the perivascular sheath could often be seen filled with the dark, red-stained fat globules.

(11) Any of the methods employed for demonstrating neuroglia shows an enormous overgrowth of fibrils, especially in the superficial layers, where it forms a dense feltwork both in the cerebrum and the cerebellum. This overgrowth is proportional to the duration of the disease. Throughout the grey and white matter the proliferated neuroglia cells of large size, with coarse and branching fibres, are seen in great abundance embracing and sticking to the ganglion cells, out of which they appear to be absorbing the phosphorized substances necessary for nuclear proliferation.

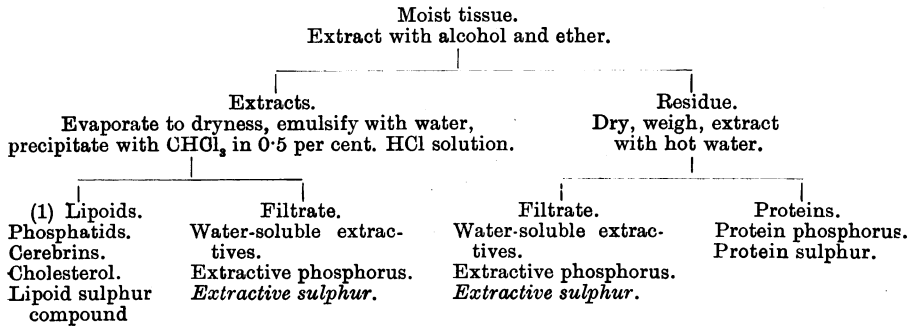
APPENDIX.

The Chemical Examination of the Brain in Two Cases of Amaurotic Idiocy, and Comparison with the Normal Brain.

By Sydney A. Mann.

In a previous investigation[1] of the brain in two cases of this disease it was shown that in the more advanced case there was a decrease of nucleo-protein which might be associated with the disappearance of the Nissl substance in the neurones, and an increase of simple protein corresponding to an increase of glia fibrils; also in both cases the lipoid sulphur and phosphorus showed a diminution, but the smallness of the size of the samples of brain matter used in that investigation made it necessary that further analyses should be made on larger samples before any conclusions could be based on the latter results.

Since that time the methods for the chemical investigation of the brain have been revised and elaborated[2] and the following research has been made on larger samples, using the methods in their amended form. The methods employed, with full analytical technique, have been already described[2] but it appears necessary to give a résumé of the scheme of analysis. By means of solvents the chemical constituents of the brain tissue are separated into four general groups: (1) lipoids, (2) extractives, (3) inorganic constituents, (4) proteins. The following scheme explains this separation:—



[1] *Archives of Neurology*, 1907, iii, p. 218.
[2] *Archives of Neurology*, 1909, iv, p. 174.

The variations of the elements phosphorus and sulphur in these groups were investigated for the following reasons. Phosphorus is the radical which seems to play the rôle in the building up of the most complex constituents of the cell, the nucleins and phosphatids, and the variation in its distribution between these and the water-soluble forms should therefore give an indication of the amount of formation or destruction of these important cell constituents. Sulphur occurs in the body in varied stages of oxidation, and the variations in the different stages probably offer a means of estimating the extent to which oxidizing reactions are taking place in the tissues. Sulphur occurs as —SH or cystin sulphur in proteins, as sulphonate or taurin like sulphur, as ethereal sulphates and inorganic sulphates; it enters the organism mainly as unoxidized or cystin sulphur and leaves in an oxidized form as inorganic sulphates.

The following forms of phosphorus and sulphur have been estimated in this investigation.

(1) *Lipoid Phosphorus.*—Phosphorus attached to the phosphatid molecules (lecithins, kephalins, sphingomyelin).

(2) *Extractive Phosphorus.*—Water-soluble inorganic and organic phosphorus compounds; previous experiments have tended to show that the water-soluble phosphorus compounds extracted from the protein fraction are mainly inorganic, but it is difficult to say how far the organic forms may not have been split up in the process of estimation.

(3) *Protein Phosphorus.*—Phosphorus in combination with proteins, nucleo-proteid.

(1) *Lipoid Sulphur.*—Sulphur in combination with lipoids; cannot be removed by cold dilute hydrochloric acid, but splits off as sulphates on prolonged boiling with dilute hydrochloric acid.

(2) *Neutral Sulphur.*—Does not split off as sulphuric acid on prolonged boiling with dilute hydrochloric acid. Does not form lead sulphide on treatment with alkali and lead acetate. Is not precipitated by phosphotungstic acid except to a very slight extent (about 5 per cent). Reacts with *α* naphthyl isocyanate like an amino acid, and represents therefore an intermediary state in the oxidation of cystin to sulphuric acid or ethereal sulphates, probably of the nature of taurin.

(3) *Inorganic Sulphur.*—Precipitated directly by barium chloride in acid solution. In this investigation the inorganic and neutral sulphur have been classed together as extractive sulphur, previous work having shown that the amounts of inorganic sulphur are so small that their investigation is a difficult matter.

(4) *Protein Sulphur.*—Sulphur in combination with proteins.

One hundred gramme samples of the minced whole brain from two cases of amaurotic idiocy, with a similar sample of the normal brain of a child of about the same age, have been investigated according to the above scheme, with the following results. Table I shows an approximation of the main groups of constituents of the brain tissue in percentage of total solids :—

TABLE I.

	Age 18 months Normal brain	Age 20 months Amaurotic idiocy Case III	Age 17 months Amaurotic idiocy Case IV
Simple protein	35·0	29·6	30·8
Nucleo-protein	10·3	13·7	10·0
Phosphatids	28·0	21·9	19·8
Cerebrins	13·9	15·9	12·2
Cholesterol	11·0	11·8	8·9
Extractives...	Not estimated.		
Ash			
Total phosphorus	1·503	1·357	1·318
Total sulphur	0·49	0·396	0·47
MOISTURE	81·52	83·44	79·31

The analysis made on 100 grm. samples of the uniformly minced brain confirm the results previously obtained from the analysis of smaller samples of the grey and white matter separately, that there is a decrease of the phosphatids in the brain of these cases, with a diminution of the total phosphorus and sulphur. The figures for the normal brain are in agreement with former analyses made on brain from children of about the same age with the exception that the nucleo-protein approximation is somewhat low.

The results of one of the cases previously reported showed a diminution of nucleo-protein with a corresponding increase of simple protein in the grey matter; this change is not apparent in the above cases in which uniform mixtures of the grey and white matter were analysed. This does not, however, negative the former result as the amount of phosphorus in the protein fraction is very small, and when the white matter (which has not been found deficient in nucleo-protein) is included, the departure from the normal is greatly increased, and unless it is very marked may be beyond the limits of chemical analysis. As further cases are obtainable this point will be further investigated on large samples of the grey matter separately.

Except in the case of phosphatids, the slight variations in the other constituents—cerebrins, cholesterol, &c.—may be explained as the result

of nutritive changes. The above figures, however, are approximations of the general groups of constituents, and a more accurate idea of the chemical abnormalities met with in the pathological brains is shown by the following Table II giving the percentage distribution of the elements phosphorus and sulphur. Tables II and III show the distribution of phosphorus and sulphur in percentage of total phosphorus and sulphur.

TABLE II.

	Normal	Case III	Case IV
Protein phosphorus	3·9	5·7	4·3
Lipoid ,, ...	72·2	62·5	58·4
Extractive ,, ...	23·7	31·7	37·2

TABLE III.

	Normal	Case III	Case IV
Protein sulphur	59·2	61·2	59·4
Lipoid ,, ...	19·4	14·8	12·5
Extractive ,, ...	21·4	24·0	28·1

The above table shows that there is *a marked relative diminution of the lipoid forms of phosphorus and sulphur with a corresponding increase of the extractive forms*, the protein and sulphur and phosphorus showing no marked change.