T A Y - S A C H S ' D I S E A S E

Study

of the symptomatology and pathology

of three atypical cases.

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THESIS

for the degree of "Doctor of Medicine"

presented by

HERBERT WATT TORRANCE, M.C.,M.B.,Ch.B.

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C O N T E N T S.

CONTENTS (Contd.)

PART I.

INTRODUCTION.

Introduction.

The work submitted in this thesis is a clinical and pathological study of three cases intermediate between the infantile and juvenile types of Tay-Sachs' disease. They form a link between the two types and present certain features which are unique on the literature on the subject. These facts coupled with the rarity of published pathological reports on atypical cases would seem to warrant this investigation.

The three patients were under the care of my late "chief", Dr. Leonard Findlay, visiting physician to the Royal Sick Children's Hospital, Glasgow. Case III was present in the wards during my residence as house-physician in the hospital. It is a great pleasure to acknowledge that the research was inaugurated at Dr. Findlay's suggestion. Dr. G. Haswell Wilson, pathologist to the hospital, kindly allowed me to investigate the material from the autopsies. The work was carried out in the hospital laboratory.

To these, my two former teachers, I would here gratefully tender my thanks for the loan of apparatus and literature, for valuable hints regarding pathological technique and the interpretation of microscopic appearances, for instruction in photography and help of every kind. Their criticism and supervision rendered valuable by their exceptional experience has in no small measure

rendered possible the accomplishment of this thesis and I owe them more thanks than I can adequately express.

To Dr. A. Maitland Ramsay I express my thanks for kindly granting me permission to make use of some diagrams from his book "Clinical Ophthalmology", and for much assistance in the ophthalmological portion of my work.

Last but not least, I take the opportunity of thanking Dr. J. W. McNee, Professor D. Noel Paton, and Dr. D. Campbell Suttie for kindly assistance in various matters.

P A R T II.

HISTORICAL SUMMARY & REMARKS ON NOMENCLATURE.

Historical Summary and Remarks on Nomenclature.

Forty years have elapsed since attention was first drawn to Tay-Sachs' disease by Waren Tay, a London opthalmologist. In 1881, under the title "Symmetrical Changes in the Region of the Yellow Spot in each Eye of an Infant," we have the first published account of the disease. It is to be noted, however, that Waren Tay did not give the disease any special name. Since then, this nameless condition has become encumbered with many synonyms - some based on a clinical foundation, others upon a pathological basis - and the investigator finds himself in a wilderness of names - e.g. "Amaurotic Family Idiocy": "Amaurotic Family Dementia": "Infantile Cerebral Degeneration": "Agenesis Corticalis or Arrested Cerebral development": and other synonyms. It will tend towards clearness of expression, the avoidance of ambiguity, the elucidation of facts, and the following of arguments discussed in this thesis, if I make a few remarks upon the history and nomenclature.

1. As already stated Waren Tay (1881) may be looked upon as the forerunner of the discovery of the disease. Being an opthalmologist, he was naturally most impressed by the peculiar ocular changes which he found.
2. In 1887, i.e. six years later, and without any knowledge of Waren Tay's report*, Sachs published a paper on a case of blindness associated with Idiocy, entitled

* Vide Sachs' article on Tay Sachs' disease in Osler & McCrae's "System of Medicine" 1910 Vol.VII p.868-874.

"Arrested Cerebral Development". Because of certain fissural abnormalities found in the brain which he examined, he considered the disease to be one of arrested cortical development, due to an "agenesis corticalis". Later he attached no importance to this observation and theory.

3. Sachs* states that Kingdon, a Nottingham oculist, was the first to demonstrate that the condition which Waren Tay had described was really part of the disease about which Sachs had written.

4. Sachs*, in 1896, recognised the <u>familial</u> element in the disease, and coined the name "Amaurotic Family Idiocy", and he quotes Higier as being the first to propose the name "Tay Sachs' Disease."

5. Other observers reported cases, and soon a symptom-complex which was said to be pathognomonic was promulgated. This will be discussed later, but suffice it to state at present, that great attention was paid to the familial factor, the "cherry-red" spot at the maculae, the mental impairment, the fact that all indubitable cases had occurred in Jews, and finally that the symptom appeared about the 3rd - 6th month of life - i.e. that it was essentially a disease of infancy.

6. The disease was considered to be sharply differentiated from all others, and it was thought to conform with punctilious exactness to the orthodox symptom-complex.

*Vide Sachs' article on Tay Sachs' disease in Osler & McCrae's "System of Medicine" 1910 Vol. VII. p.868-874.

Being rather a rarity*, few cases were reported, and so for a time no trouble was caused. But as more cases accumulated, investigators found that some did not conform in every detail to the accepted syndrome. The slightest variations prompted the coining of sub-types of the disease (i.e. Infantile and Juvenile type of Tay-Sachs) or in some cases of entirely new names. The factors and symptoms mentioned in the preceding paragraphs are those concerning which there has been most controversy.

7. In 1897, R. D. Batten gave a description of two brothers with macular changes (but not the characteristic "cherry red spot" of Tay-Sachs' disease). Moreover, the onset of the disease was at the age of 14 years - not in infancy as in Tay-Sachs' - and there was no mental impairment as in Tay-Sachs'. Such a case is sometimes referred to as the Juvenile Type of Tay-Sachs' disease, in contradistinction to the Infantile Type of Tay-Sachs' or Tay-Sachs' proper. By others, these cases are referred to thus:-

(1) Clark -- "Familial macular degeneration without Dementia."

(2) Darier - "Familial Macular Degeneration."

(3) Batten & Mayou - "Family Cerebral Degeneration with Macular Changes."

(4) Oatman - "Macular Type of Familial Degeneration" (there being no mental weakness).

This he carefully distinguished from what he

*Osler - "Principle and Practice of Medicine" 1920, p.932 quotes Naville as collecting 100 reported cases up to 1917.

termed the "Maculo-cerebral" type of familial degeneration in which the pathological process attacked not only the retina, but also the brain and so led to mental impairment.

8. In 1903, under the title "Cerebral Degeneration with Symmetrical Changes in the Maculae in two members of a family", F. E. Batten* described a family in which two brothers had symmetrical changes in the maculae but not typical "cherry-red spots" as in an infant suffering from Tay Sachs disease. Mental deficiency was present but the onset of the disease was at 4-6 years of age and not in infancy. Such cases would be called:-

   (1) By Clark - "Familial Macular Degeneration with Dementia".

   (2) By Gifford -"Juvenile type of Amaurotic Family Idiocy."

   (3) By Oatman - "Familial Maculo-cerebral Degeneration."

9. It was Vogt who, in 1905, gave the name Juvenile Amaurotic Family Idiocy to those cases in which the disease began in youth instead of in infancy. He also pointed out that there was no predilection for Hebrews in the juvenile type. His belief was that the infantile and the juvenile form of Tay-Sachs' disease represent different degrees of the same process.

10. Mott suggested the name "Amaurotic Dementia" rather than Amaurotic Idiocy, as the macroscopic appearance of the brain was unlike that of an idiot or imbecile.

*Confusion is caused unless it is observed that there are two different investigators, both with the surname BATTEN, who have written about Tay Sachs disease.
(1) R.D.Batten described the first case of what Oatman terms the "macular" type of the disease. (1897)
(2) F.E.Batten described the first "maculo-cerebral" case (1903).

11. Some cases, e.g. Kuffler's Case IV - show changes at the periphery of the fundus and none at the macula. Here again a difficulty arises as to nomenclature. Can any name including the word "macular" be used as a label for such cases? Omitting for the present the question of the presence or absence of dementia, any names such as "Familial Macular Degeneration" or "Familial Maculo-Cerebral Degeneration" would be misleading. Gifford therefore suggests the name "Familial Retino-Cerebral Degeneration with Infantile and Juvenile Forms" as one which would "describe the whole family". Those who lay stress upon the presence or absence of mental symptoms, however, would object to the inclusion of the term "cerebral" (in the phrase "retino-cerebral") if no mental defect were present.

12. The investigator, who would sharply differentiate the various types of this familial degenerative disease (which I will simply term Tay-Sachs' disease) as distinct and separate entities, finds this to be an impossibility. As shown later in this paper, there may be several different types in one family (e.g. Kuffler's cases). Surely they are not distinct and separate diseases. Are they not members of one large group of familial neuropathic disease? As Darier remarks, "It is probable that the more precocious the macular changes, the more likely are the cerebral functions to be affected: when the

eye symptoms do not appear until 12-14 years, the brain is not affected. Again, one may note in general that these affections are so much the graver, the younger the age at which they begin."

In reviewing the literature for this thesis, I set out definitely to differentiate the various types of the disease. This I have found to be an impossibility. Some cases present certain features belonging to one type, and certain features belonging to another type. It became a matter of great difficulty to decide to which type such irregular cases should be relegated. In this paper, the term "Infantile Tay-Sachs" may be taken as referring to cases showing marked similarity to Tay-Sachs' original symptom-complex and especially to the fact that the disease commenced in infancy (under one year) and showed a predilection for Jews. In contra-distinction to this infantile type the "Juvenile Tay-Sachs" refers to those in which the onset of the disease was after the first year of life and showed no marked predilection for the Jewish race.

Infantile Amaurotic Family Idiocy is synonymous with Infantile Tay-Sachs: Juvenile Amaurotic Family Idiocy with Juvenile Tay-Sachs, but I prefer the terms Infantile, or Juvenile Tay-Sachs to their respective synonyms, as idiocy is not always present.

The cases described in this thesis are of the Juvenile type, the onset of disease being shortly after one year, and in Gentiles. They are the youngest juvenile cases on record in which a pathological examination has been made, and I venture to suggest that they form an important link

and help to bridge the gap between the infantile and juvenile types of Tay-Sachs' disease.

PART III.

SYMPTOMATOLOGY.

CLINICAL HISTORY OF CASE I.

D.H., a male child, aet. 4 years and 4 months, was admitted to the Royal Hospital for Sick Children, Glasgow, on 15th January, 1919, under the charge of my "chief" Dr. Leonard Findlay.

COMPLAINT.

Gradual mental and physical deterioration of about $3\frac{1}{3}$ years' duration.

FAMILY HISTORY.

Father, aet. 29 years, the eldest of a family of seven, alive and well.

Mother, aet. 28 years, the youngest of a family of nine, alive and well.

Married five years ago. No history of Luetic disease.

Neither of the parents are Jews.

No history of nervous disease, insanity, epilepsy, or tuberculosis in ascendants or collaterals.

Three children in family:-

1. "D.H." - patient.
2. "M.H.", girl, aet. 3 years, began to deteriorate at 1 year.
3. "A.H."., girl, aet. 1 year, has shown signs of deterioration during last fortnight. *

* These are respectively Cases I, II & III, which form the subject of this thesis.

PREVIOUS HEALTH.

Normal birth, and healthy when born. Never breast fed, as child refused mother's milk. Fed on Robinson's Patent Barley for one year, and then on the "run of the house." No history of rash, rhinitis, conjunctivitis, jaundice, or convulsions. Cut first tooth at five months, sat up at eight months, and walked at one year when he also began to talk. Seemed quite a normal child until this time, was bright and took an interest in his surroundings.

HISTORY OF PRESENT ILLNESS.

Shortly after the patient was one year old, it was noticed that he "blinked" considerably, and that his teeth began to decay almost as soon as they erupted. He became apathetic and listless, kept his mouth open, and ceased trying to talk, walk, stand, or take any interest in his surroundings. The muscles of his legs became flabby and his whole body thinner. After scarlet fever at $1\frac{10}{12}$ years, his mental and physical retrogression became more rapid. Child always cried a great deal until the age of 2 years, but later became much quieter. His mother states that he can hear and see, but does not understand what is said to him and also that he has some difficulty in swallowing, has a good appetite and tends to be constipated. There is no history of convulsions or fits of any nature.

CONDITION ON ADMISSION.

General Condition. Fair sized but much emaciated boy. Length $36\frac{1}{4}$". Weight 19 lbs. 8 oz. Circumference of head $18\frac{1}{2}$". Unable to walk, stand, sit, or feed himself.

Mentality. Face lacks expression. Very apathetic and practically imbecile. Takes no interest in his surroundings. Does not attempt to catch objects.

Special Senses.

Eyes. Slight mystagmus. Pupils are moderately dilated, equal in size, circular in shape, and react normally to light and on accommodation. Patient can see.

Opthalmoscopic examination reveals optic atrophy in both eyes, and vessels are badly defined. A small patch of pigment is seen on the temporal side of the disc (but not at the macula) in the right eye. There are no appearances of macular changes in either eye.

Ears. Patient can hear, but cannot understand when spoken to.

Nose. Nothing abnormal detected.

Nervous System.

No nuchal rigidity or retraction of the head.

Arms:- Spastic. Triceps, biceps and supinator jerks on both sides are very active.

Legs:- Flaccid, but occasionally seen slightly spastic. Both knee jerks are present, equal, and not exaggerated. Positive Babinski's sign elicited on left side.

No ankle clonus.

Sphincters of bladder and rectum are incontinent.

Circulatory System.

Pulse - 104 per minute, regular, and of good quality.

No enlargement of praecordial dulness.

Heart sounds pure.

Name David Hartley.

Age 4 4/12 yrs.

Ward 4.

Disease

Result

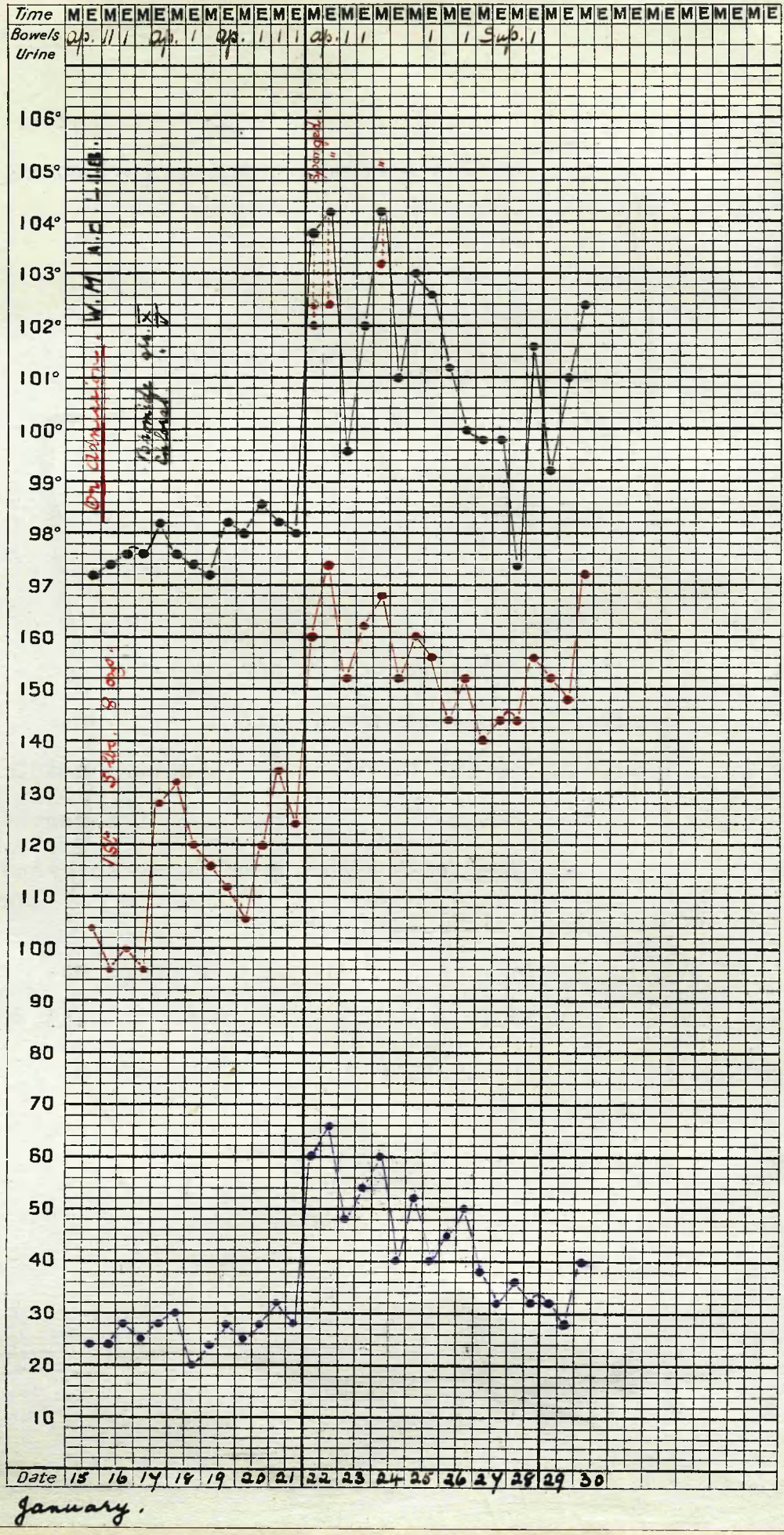
TEMPERATURE

PULSE

RESPIRATION

DATE OF ADMISSION

15 . 1 . 19.



Digestive System.

Tongue moist and furred. Teeth deficient and very much decayed. Throat - clear. Abdomen - nothing abnormal detected.

Lymphatic System.

Slight general enlargement of lymphatic glands.

Respiratory System.

Respirations - 24 per minute. Lungs normal.

Genito-urinary system.

Microscopic and chemical examination of urine reveals nothing abnormal.

Thymus gland.

No enlargement detected on percussion.

Von Pirquet Cutaneous Tuberculin Reaction.

(1) With bovine tuberculin - positive reaction.

(2) With human " - negative reaction.

Wassermann Test with blood gave negative result.

Cerebro-Spinal Fluid.

Fluid is clear and under very low pressure. No deposit on centrifugalising. Fluid reduces Fehling's Solution. On microscopic examination no cells and no organisms found.

SUBSEQUENT HISTORY AFTER ADMISSION.

Child was very irritable and cried during the nights. He had to be fed by hand and passed urine and faeces in bed. Two nights after admission he was so restless and screamed so much that chloral and bromide were administered.

As will be seen from the accompanying chart, on the

evening of the seventh day in hospital, his temperature rose to 102.8° F., with pulse rate of 160 per minute, and respirations 40 per minute. Next day, examination of the chest revealed tubular breathing at the left apex, moist rales at the right apex behind, and wheezing all over the rest of the lungs. He could not be roused and took no interest in anything.

During the next few days he emaciated very rapidly, slept constantly, and was more or less unconscious. Lumbar puncture revealed the cerebro-spinal fluid to be under very low pressure, clear, with no visible deposit after centrifugalising. It reduced Fehling's Solution. No cells or organisms were found on bacteriological examination.

The child's general condition became gradually worse, and fifteen days after admission he died.

Opthalmoscopic examination of the eyes four days before death revealed no further change than on admission.

CLINICAL HISTORY OF CASE II (Patient M.H.)

M.H., aet. $3\frac{1}{12}$ years, sister of patient D.H., admitted to Royal Hospital for Sick Children on 25/1/19 under the care of Dr. Leonard Findlay.

FAMILY HISTORY.- as in Case I.

HISTORY OF PREVIOUS HEALTH.

Easy birth, non-instrumental. Child was apparently healthy when born. No history of rash, rhinitis, conjunctivitis, convulsions or jaundice. Breast fed for two weeks, then feeding supplemented by bottle (milk and water) until age of 10 months, after which diet consisted of the "run of the house". Cut first tooth at $5\frac{1}{2}$ months, sat up at 8 months, began to talk at 9 months, and walked at 1 year. Appeared to be perfectly normal until this time. No history of child suffering from any of the Exanthemata or other illness.

HISTORY OF PRESENT ILLNESS.

Shortly after the age of 1 year, fine oscillating "up and down" movements of both eyeballs were noticed and this was specially marked when patient was looking at any object. She ceased to make any progress in walking and talking, and thereafter gradually retrogressed. Her teeth seemed to decay almost as soon as they erupted. At 2 years of age, she was subject to severe "fits of crying" - diurnal

and nocturnal - which gave her a cyanosed appearance during these seizures. About this time also she had two severe attacks of vomiting within a week of each other, which weakened her considerably. Since then, she has been unable to walk, stand or even sit up, and although she seems to understand what is said to her, mother states that child is not so bright now as at one year, and has never played with toys since then. Parents think child's sight and hearing have always been good. She takes her food with avidity, but cannot chew well on account of her bad teeth. Bowels generally constipated.

CONDITION ON ADMISSION.

Fair sized and moderately well nourished child, fat but flabby, weighing 22 lbs. 2 oz., and measuring 31¼" in length. There seems to be an increase of subcutaneous tissue with poor musculature. Her skin is healthy and colouring good. Forehead is narrow and circumference of head 19¼". She can neither stand nor sit.

SPECIAL SENSES.

Eyes. Child can see to a limited extent. Mystagmus - vertical, lateral and rotatory is present.

Pupils are equal, circular and moderately dilated. React normally to light and on accommodation.

Opthalmoscopic examination reveals double optic atrophy but no macular or pigmentary change.

Ears. Child can hear to a limited extent.

Nose. Slightly saddle-shaped.

NERVOUS SYSTEM.

1. Intellectual Functions. Child behaves like a child of nine months. Does not evince the slightest interest in anything, and does not seem to understand what is said to her.

2. Motor Functions. No definite paralysis detected in any region, but she can neither walk, stand, nor sit. Can grasp objects. The general musculature is poor. There is no nuchal rigidity, but the limbs, especially the upper ones, are somewhat spastic.

   Chvosteks sign is easily elicited.

   Electrical Reactions (Right Ulnar Nerve)

   K.C.C. = 0.4 m.ap.

   K.O.C. = 5.0+ m.ap.

   A.C.C. = 1.0 m.ap.

   A.O.C. = 0.5 m.ap.

3. Reflexes.

   Triceps, biceps, and supinator jerks of both arms exaggerated.

   Knee jerks are equal and exaggerated.

   Positive, Babinski present in both feet.

   Ankle clonus not elicited.

   Abdominal reflexes not elicited.

4. Sensory Functions.

   As far as this could be tested, sensation is unaffected.

Circulatory System.

Pulse rate - 104 beats per minute, and quality fairly good.

Cardiac examination revealed nothing abnormal.

Digestive System.

Mouth - open most of the time.

Tongue - clean. Teeth - deficient and carious.

Throat - negative. Abdominal examination negative.

Lymphatic System.

There is some enlargement of glands in the submaxillary region.

Respiratory System.

Breathing is quiet and regular, 34 respirations per minute.

No cough. Lungs normal.

Genito-urinary system.

Physical, chemical, and microscopic examination of the urine negative.

Wassermann Blood Test - Negative result.

Von Pirquet Test - negative with bovine and human tuberculin.

Cerebro-Spinal Fluid.

Fluid clear and under slight pressure.

No cells and no organisms found. Culture remained sterile.

SUBSEQUENT HISTORY AFTER ADMISSION.

Three days after admission, the legs were noticed to be quite flaccid, although previously they had been spastic. The arms were still definitely spastic. All the reflexes remained as before. The child was always very noisy,

Name Mary Hartley.

Age 3 years

Ward 4

Disease

Result Died.

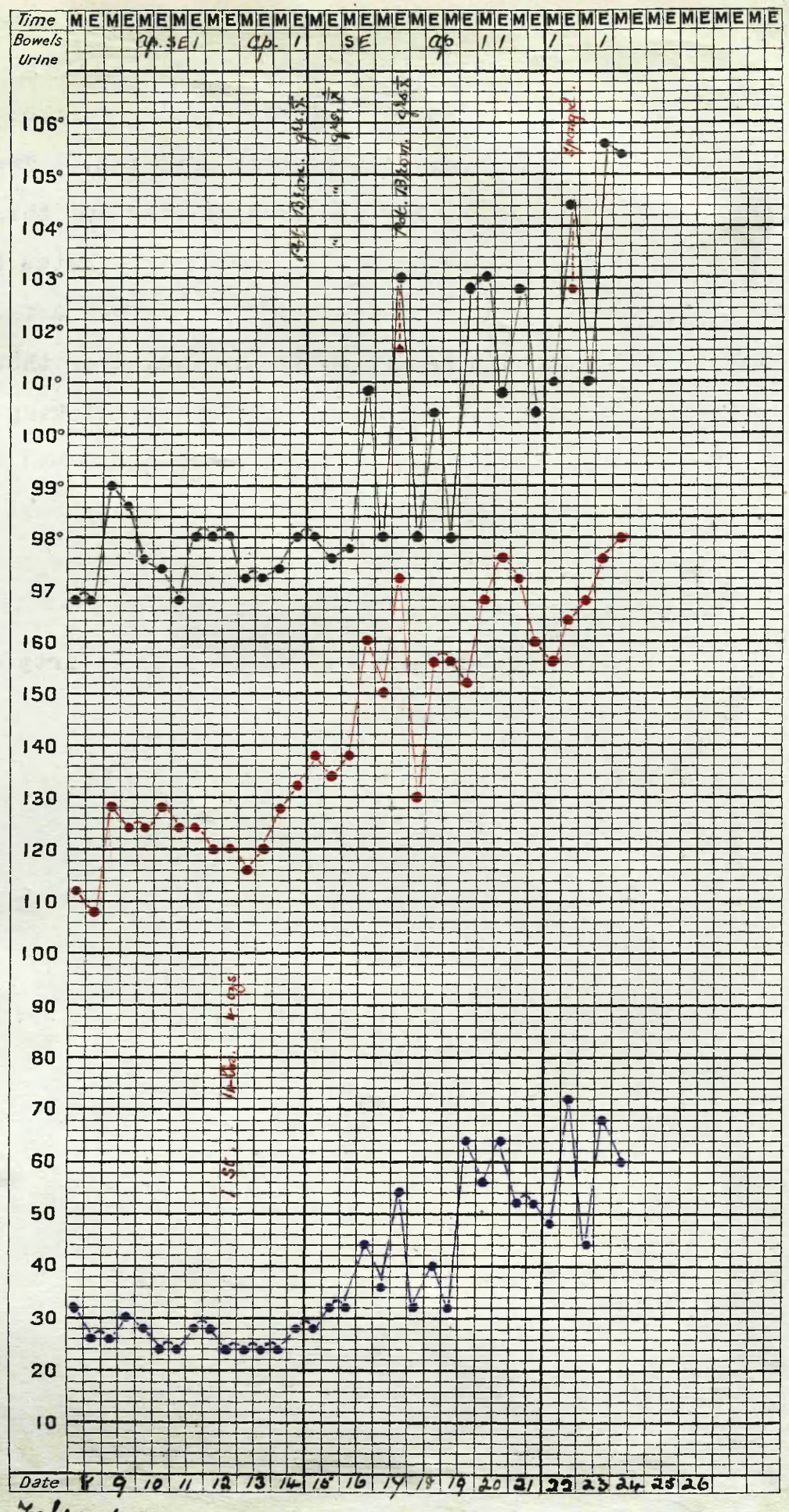
TEMPERATURE

PULSE

RESPIRATION

DATE OF ADMISSION

25. 1. 19.



especially during the night, and on two occasions required Potassium Bromide. She deteriorated further mentally, and ceased to take any interest in anything. Twenty-two days after admission, her temperature rose and this was accompanied by a rise in the pulse and respiratory rates (vide accompanying chart). Next day, definite dulness was detected at the right apex, back and front, while the R.M. over that area in front was tubular and accompanied by moist clicking rales. The chest elsewhere was clear. Fever and rapid breathing continued, and on 21/2/19 (28th day in Hospital) dulness was detected at the base of left lung. Urine contained a cloud of albumen.

Patient died at 5.30 a.m. on 24/2/19, thirty-one days after admission to Hospital.

CLINICAL HISTORY OF CASE III (Patient "A.H.").

A.H., - female - is the third and youngest member of the H. family. She was an inpatient of the Royal Hospital for Sick Children on three different occasions under the care of Dr. Leonard Findlay. The first date of admission was 29/3/19 when she was $1\frac{3}{12}$ years old. She had been seen for a few moments on two previous occasions, however, when she accompanied her mother who was then visiting Cases I and II.

1st occasion when seen:- 15/1/19. Child then aged one year. Examination shewed that she had slight nystagmus, and kept her mouth open. Mother stated that this had been present for two weeks.

2nd occasion when seen:- 6/2/19. Severe nystagmus and pallor of both optic discs noted.

3rd occasion when seen:- 29/3/19. aet. $1\frac{3}{12}$ years. Admitted as inpatient to Royal Hospital for Sick Children.

FAMILY HISTORY - as in previous cases, except that Cases I and II had died when case III was admitted to Hospital.

PREVIOUS HEALTH.

The child was born at full term and the labour was easy and non-instrumental. The birth weight is unknown. She was vigorous and healthy when born and was breast fed for two months, then on Allenbury's Food No. I till four months old, followed by Allenbury's No. II till 1 year old, and thereafter "the run of the house."

The first tooth was cut at 7½ months, she sat up at 9½ months, began to walk round the chairs at 1 year, but so far has never managed to walk alone. When about 13 months old, she could say a few words. Child has never had snuffles, rash, jaundice, convulsions, or any illness whatever.

HISTORY OF PRESENT ILLNESS.

As in the case of her elder brother and sister, the present illness dates from the time she was just over a year old. Previous to that, the parents were satisfied with the progress the child made, and thought she was quite normal. The first observation made was the "up and downward movement of the eyeballs" which were almost incessant for two months and then became less marked. Next "the teeth began to get black and soon broke away." It was now manifest to the parents that the child was making no further efforts to talk or walk, and that she was making no progress whatever. During the past three months she has tended to keep her mouth open when asleep. She occasionally plays with her toys, but soon gets tired of them. Parents state she can hear and see, and recognises her relations. Bowels are very constipated. She sleeps soundly and takes her food well.

CONDITION ON ADMISSION. (29/3/19)

Fair sized, well developed, sturdy female child with healthy skin and good colouring. Body length = 29¾". Weight = 19 lbs. 14 oz. Square head 19¼" in circumference.

Anterior fontanelle is slightly patent. Palate highly arched. No congenital malformations.

SPECIAL SENSES.

Eyes. Palpebral fissures are horizontal. Lateral and rotatory mystagmus present. No strabismus. Pupils equal, circular and moderately dilated. They both react to light and on accommodation but the left more sluggishly than the right. Optic discs are unduly pale especially the left, the periphery of which is unduly pale. No macular or pigmentary changes. Child can see and occasionally takes a little interest in her surroundings.
Ears and Nose - negative.

NERVOUS SYSTEM.

1. Intellectual Functions. She occasionally pays attention to people and things, and tries to say a few separate words.
2. Motor Functions. Can sit up but cannot stand unsupported. Can grasp objects, but not as a normal child should do. There is slight spasticity of the arms, but none of legs. No ataxia.
3. Reflexes. Arm and knee jerks - normal. No ankle clonus. Babinski's sign present in both feet. Chvostek's sign is present.
4. Sensation. No anaesthesia or sensory disturbance of any kind as far as one could judge, although naturally the tests could not be carried out very satisfactorily in such a patient.

Circulatory System.

Pulse, 120 beats per minute and of good quality.

Heart negative.

Digestive System.

She lies with her mouth open. No adenoids. She has eight teeth (the four upper and the four lower incisors) and they are carious. Tongue clean. Throat negative.

Abdominal examination negative.

Lymphatic System.

No glandular enlargement.

Respiratory System.

The respirations, 24 per minute, are regular and quiet.

Lungs normal. No cough.

Genito-Urinary System.

Physical, chemical and microscopic examination of the urine negative.

On this occasion patient was detained in hospital for one week and during that time nothing of further interest was noted. As compared with other children of the same age, she was certainly less alert. She only sat up occasionally to play with her toys, and at night would call out a great deal before going to sleep. She took her food well. Dismissed 4/4/19.

4th occasion when seen:- 25/6/19 to 28/6/19.

Since last dismissal (4/4/19) patient has deteriorated further, and now makes practically no attempt at walking, but can sit and catches objects offered to her. She has become duller, and lately, subject to fits of screaming during the night. She has a more vacant expression, keeps her mouth open, is very irritable, and cannot be easily entertained. Cannot feed herself. Measurement reveals that she has not grown since first coming under observation and during the last 2½ months she has lost 14 oz. in weight (present weight - 19 lbs.)

Eyes. Vertical mystagmus. Pupils equal, circular, normal in size. React to light and on accommodation. Both optic discs very pale on opthalmoscopic examination, and very sharply defined in outline. very little abnormal to be seen in the retinal blood vessels, but towards the periphery of both fundi, there is want of pigmentation.

Nervous System. No spasticity of limbs. Reflexes normal. Babinski's sign positive in right foot. No Chvostek's sign.

Electrical reactions

K.C.C. = 0.6

A.C.C. = 2.0

A.O.C. = 0.8

K.O.C. = Tet. = 4.0

5.0 +

Von Pirquet. Negative.

Urine. Negative.

Wassermann Reaction. Negative.

Name { Anne Hartley.

Age 2 years.

Ward 4.

Disease

Result Died.

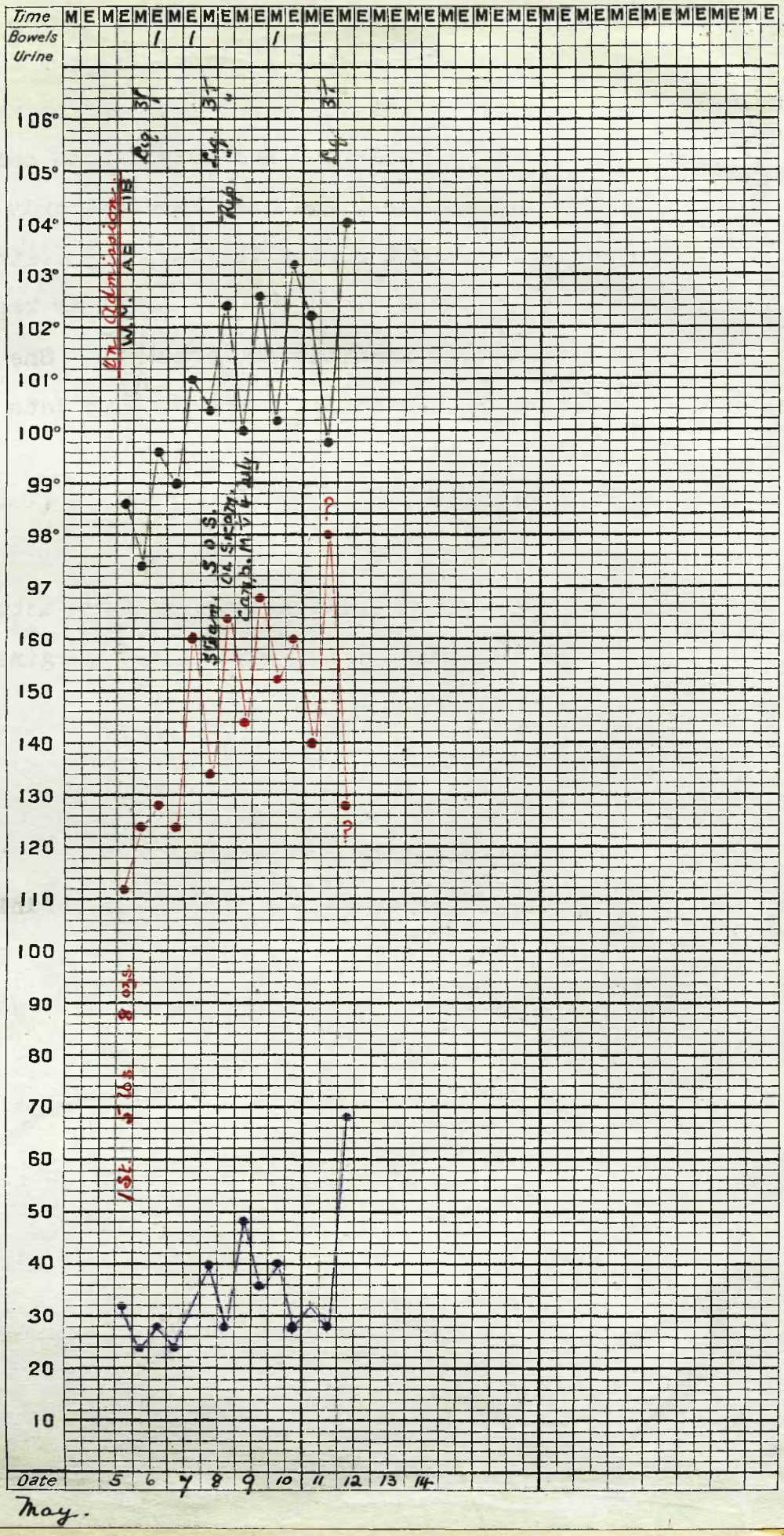
TEMPERATURE

PULSE

RESPIRATION

DATE OF ADMISSION

5. 5. 20.



5th occasion when seen:- Admitted 5/5/20.

Child, although now $2\frac{5}{12}$ years old, cannot walk, talk or pay attention to anything. Her body length being now $30\frac{1}{4}$" and her weight $19\frac{1}{2}$ lbs., she has therefore only grown $\frac{3}{4}$" and put on $\frac{1}{2}$ lb. in weight during the last $10\frac{1}{2}$ months. The anterior fontanelle is now closed. Her mouth is kept open, her teeth are carious, no adenoids are present. She can lift toys placed before her but in a few moments lets them drop in an aimless fashion.

Eyes. She can see and seems to recognise her parents. There is definite lateral mystagmus. The pupils are dilated and react to light but not very actively. The fundi are pale and there is pigment at the margins but no macular change is visible.

Chest and Abdomen. Negative.

Urine - negative.

Von Pirquet reaction - negative.

On the day after admission, there was definite spasticity of both arms, but the legs were flaccid. The abdominal reflexes were not elicited. No ankle or patellar clonus. Both knee jerks were exaggerated. Positive Babinski's sign present in both feet. No Chvosteks sign.

From this date - 6/5/20 - the temperature and pulse rose steadily, a slight cough developed, the tongue became dry and furred and much purulent mucus collected at the back of the throat. She developed broncho-pneumonia and died on 12/5/20.

Summary of three Clinical Histories.

An account is given of a childship of three, all affected with a similar disease.

The family history is a negative one, there being no history of consanguinity, nervous troubles or luetic disease in the parents, ascendants or collaterals.

Previous Health of Patients.

Obstetric histories good. Birth non-instrumental. One child was entirely bottle-fed, the other two partly breast, partly artificially fed. Growth and development were normal until the age of 1 year, during which time they had had no illnesses (except Case I scarlet fever).

Present Illness. The eldest child was a male, the other two females. In each case the onset of the disease dated from the age of one year. The cases resemble one another closely, hence a combined symptom-complex may be given.

The disease was characterised by a progressive mental and physical deterioration. The initial observations were nystagmus, dental caries, cessation of attempts at walking and talking, the later symptoms being apathy, listlessness, "screaming fits", and progressive mental enfeeblement.

Condition on Admission to R.H.S.C.

No gross congenital deformities. The first or eldest case was emaciated, the other two of fair size and development. All showed a varying degree of mental

impairment as evinced by the inability to take any interest in their surroundings or to talk; the irritability, "screaming fits", and the apathy. There was also physical enfeeblement. None of the children could stand unsupported and even sitting was an impossible accomplishment (except in Case III). The arms were spastic, the legs only occasionally so. The arm and knee jerks varied, but on the whole were exaggerated. Babinski's sign was positive. The sphincters of the bladder and rectum were not under control.

Eyes. Nystagmus present. Pupils negative. Double optic-nerve atrophy. No macular changes. In Case I, a patch of pigment was present at the temporal side of the disc (but not at the macula): in Case II, there was no pigmentary change, while in Case III pigmentary changes at the periphery of the fundus were observed on the last occasion when examined.

Sight and hearing were present in a limited degree but the children did not understand what was said to them.

Chest and abdominal examination negative.

The von Pirquet cutaneous tuberculin reactions were negative with bovine tuberculin (except in Case I) and also with human tuberculin.

All results of urinary and cerebro-spinal fluid examinations as well as the Wassermann tests were negative.

Subsequent History.

The condition of each child became progressively worse but death was due to an intercurrent disease. In each case the causa mortis was broncho-pneumonia. The ages at death were respectively $4\frac{4}{12}$, $3\frac{2}{12}$, and $2\frac{5}{12}$ years.

Symptomatology.

The symptomatology of any disease must be considered hand in hand with its pathology. Nowhere is this more important than in nervous diseases, because in them emphasis must be laid upon the fact that:-

(1) Similar symptoms may be produced in two patients by two entirely different pathological processes.
e.g. Syphilis and tuberculosis are two entirely different diseases and yet by involving similar parts of the brain, they may cause very similar symptoms.

(2) Conversely the same pathological process in two different patients may produce entirely different symptoms.
e.g. a syphilitic lesion near the Rolandic area in one patient would cause symptoms differing markedly from those caused by a similar syphilitic lesion involving some of the cranial nerves.

It is not uncommon to find cases, the clinical reports of which closely resemble Tay-Sachs' disease but which did not suffer from this disorder. There are disturbances of vision in children accompanied by mental impairment and physical weakness which may easily carry a wrong diagnosis of Tay-Sachs' disease if due care is not exercised in eliminating syphilis and congenital conditions. Pre and post natal cerebral palsies, myoclonic epilepsy (familial), (vide Osler & McCrae's "Principles and Practice of Medicine" 1920 p. 932), Congenital Amblyopia,

(Maitland Ramsay p. 399), the "Hereditary Macular Anomaly" referred to by Oatman (p.231) and other conditions might cause some difficulty in diagnosis.

To illustrate this, Stock's four cases are by some classified as examples of juvenile Tay Sachs' but the clinical histories suggest a syphilitic basis. By most writers, syphilis is not regarded as being an etiological factor in Tay Sachs' disease, and hence Stock's cases should remain unclassified for the present.

A negative Wassermann Reaction was obtained in each of the three cases described in this thesis. The question of birth traumatism, congenital forms of idiocy, hydrocephalus, and hereditary taints were all eliminated and I submit that these cases can justly be classified as examples of juvenile Tay Sachs. Certainly the familial factor is very marked.

In order to facilitate the discussion of the part played by these cases in bridging the gap between the infantile and juvenile types, one may consider the following:-

I. Summary of symptoms in the Infantile Type.
II. " " " " " Juvenile "
III. Relationship of the three cases described in this thesis to the above types.

I. Summary of Symptoms of Infantile Tay-Sachs Disease.

The following is Sachs' summary as given by him in Osler & McCrae's "System of Medicine".

" 1. A mental impairment during the first months of life leading to absolute idiocy.

2. Paresis or paralysis of the greater part of the body, which may be either flaccid or spastic.
3. The reflexes may be normal, deficient, or increased.
4. A diminution of vision terminating in absolute blindness ("the cherry red spot" in the region of the macula lutea and later a simple optic nerve atrophy).
5. Marasmus and a fatal termination, as a rule, before the age of 2 years.
6. The occurrence of the affection in several members of the same family.

In some, but not in all of the cases -

7. Nystagmus.
8. Strabismus.
9. Hyperacusis.
10. Convulsions. "

Add to this the fact that the children are apparently in perfect health at birth and generally remain so until 3-6 months, also the racial predisposition (Jews), and one has a fairly complete picture of the disease.

II. Summary of the Symptoms in Juvenile Tay-Sachs.

This is often referred to as the Spielmeyer-Vogt type of the disease. I give the following translation* by F. E. Batten of Vogt's clinical picture.

"A hitherto healthy child (usually more than one in a family without any special race disposition) becomes ill

* F.E. Batten, Quart. Journ. Med. July 1914. p.445.

during the school age, sometimes between the age of fourteen and fifteen. The children in the same family become affected in the same year of life. The beginning is gradual: the first symptom is usually the failure of sight, but loss of mental capacity or motor weakness may first appear. The loss of sight passes in the course of months to a complete blindness. Ophthalmoscopically there is atrophy of the papilla. The mental development stands still, or goes back. The children do not progress in the school, soon lose the acquired capacity to read and write, and, lastly, of speech. They become unsocial, dirty in eating, unclean in habits, and totally inattentive to their surroundings, no longer know their own mother or make articulate speech. Little by little they become completely demented. Hand in hand, in most cases, there is diminution of motor function,-at first weakness in the limbs and back, later complete paralysis. The paralysis is sometimes flaccid, sometimes spastic, leading to complete helplessness, atrophy, and death."

From the above clinical picture of the <u>juvenile</u> type, it will be seen that there is a close resemblance to the <u>infantile</u> type. There are, however, three differential points, viz:-

(1) There is no partiality towards the Jewish race.

(2) The macular changes are not pathognomonic and do not conform to the typical description of "cherry-red spot in the centre of a whitish grey oval patch at the region of the macula lutea." In fact, some cases, (e.g. Kuffler's case No. IV and my own) show

no changes exactly at the macula although there are other fundal changes present. The ophthalmoscopic changes could therefore be referred to with more freedom as "retinal" rather than "macular".

(3) The disease occurs later in life - hence the inclusion of the qualifying adjective "juvenile" in contra-distinction to "infantile".

Oatman (1911) subdivided this form of degenerative disease into:-

(1) The "maculo-cerebral" type, in which both retina and brain are attacked.

(a) The term is meant to convey the idea of failure of vision combined with failure of intellect.

(b) The onset of the disease is between the 5th and 7th years - the period of second dentition.

(2) The "macula" type, in which the retina is attacked by the pathological process but the brain escapes.

(a) This term is meant to convey the idea of eye symptoms without the addition of dementia.

(b) The onset of the disease is between 14 to 16 years - the period of puberty.

Some authors (e.g. Clark 1918) accept this classification, others do not (e.g. Gifford 1912). This classification implies that macular changes are always present. This is not so! Under what group can one place cases in which there are retinal changes but no macular changes? In the same childship one may get cases with abnormal macular appearances, and others with ophthalmoscopically apparently normal maculae.

If one takes the family described by Kuffler, the results may be tabulated thus:-

Child.	Presence or absence of imbecility.	Presence or absence of optic nerve atrophy.	Was periphery of retina affected.	Macular changes.
No. 1	Yes.	Yes.	Yes.	Dirty red spot at the macula.
No. 2	Yes.	Yes.	Slight. (at least, spots faded towards the periphery)	Coarse spots at the macula.
No. 3	Almost none	Yes.	No:- at first. Yes:- later when there was some fine pigmentation.	Yes:- at first spots at the posterior pole. Yes:- later when the macula had a reddish spot in the centre of a yellowish area with radiations at its margin.
No. 4	No.	Slight.	Yes.	No change.

From this table it will be seen that here in the one family, children suffering from the same disease, presented slightly differing symptoms and the difficulty of differentiating the types is obvious.

Case I. Mental + Macular + Peripheral Retinal Changes.

Case II. Mental + Macular + Slight Peripheral Retinal Changes.

Case III. Slight mental + early macular + late Peripheral Retinal Changes.

Case IV. No mental + no macular + slight peripheral Retinal Changes.

The table also serves to illustrate Darier's remark that "the more precocious the macular changes, the more likely are the cerebral functions to be affected".

Again, taking the cases described in this thesis:*

Case.	Presence of imbecility.	Presence of optic atrophy.	Changes at periphery of fundus.	Macular Changes.
No.1	Yes.	Yes.	Patch of pigment.	None.
No.2	Yes.	Yes.	None.	None.
No.3	Yes.	Yes.	Pigmented at last examination.	None.

Although optic atrophy was present in all these cases, none showed changes at the macula. It is possible that if the children had lived longer, instead of being carried away by an intercurrent disease (broncho-pneumonia), some changes might have become visible at the maculae.

III. The Clinical Relationship between the Infantile and Juvenile Forms of Tay-Sachs' Disease and the part played by the present cases in forming a connecting link.

Clinically, a gulf would seem to separate the infantile and

* At Dr. Findlay's request, all the patients were examined by Dr. A. Maitland Ramsay and he substantiated the ophthalmological findings.

juvenile groups: pathologically only a crevice. The factors chiefly responsible for the breech in clinical continuity are the differences in age incidence, race proclivity, and eye symptoms. Are these sufficient to separate the two types? Is there not a possibility of bridging the gap with connecting links? In order to answer such questions, I had to make a thorough search through as many reported cases as possible, of both types of the disease. I would here point out that the number of reported juvenile cases is considerable - far more than certain articles would lead one to imagine. The juvenile group is not as clearly defined as the infantile one, and my attempt to arrange the cases for descriptive purposes under such headings as 'macular' and 'maculo-cerebral' has been abandoned. The following is an incomplete list of some juvenile cases, a precis of each case is impracticable.*

(1) R. D. BATTEN. (2 cases)

Trans. Ophth. Soc. 1897, XVII, 48.

(2) F. E. BATTEN. (7 cases)

(a) 2, in Ophth. Trans. U.K. 1903, xxiii, 390. Their subsequent histories are given in Proc. Roy. Soc. Med., 1915, viii, Ophth. Sect. p.72.

(b) 3, in Proc. Roy. Soc. Med., 1915, VIII, Ophth. Sect. p.72.

* The references are given at the end of the thesis but some are incorporated in the text where confusion might arise.

(c) 2, Fred B. and Henry B. These are mentioned in the "Summary" in Quart. Journ. Med. 1914, VII, p.451.
The cases mentioned in the "body" of the paper are the same as under (b)

(3) BEHR. (6 cases)

Monatschr. f. Psych. 1910, XXVIII, p.327.

(4) BIELSCHOWSKY (3 cases)

Deutsche Zeitschr. f. Nervenheilk, 1913, 1, p.7.

(5) CLARK. (2 cases)

(6) DARIER. (5 cases)

(7) FIRÜKOWA. (2 cases)

(8) GIFFORD. (1 case)

He also refers to 5 other cases about which some doubt is expressed.

(9) GORDON. (2 cases)

(10) HIGIER. (8 cases)

In Deutsche. Zeit. f. Nervenheilk IX p. I four sisters are described with the disease.
In Deutsche Zeit. f. Nervenheilk XXXI p. 231 four other cases are described.

(11) ICHIKAWA (1 case)

(12) KUFFLER (4 cases)

(13) MAYOU (3 cases) 1904.

(14) MÜLBERGER (2 cases)

(15) NETTLESHIP (1 case)

In his paper "On some cases possibly allied to Tay Sachs' Infantile Retinitis" Trans. Ophth. Soc. 1908 p. 76, he describes thirteen patients but only No. 9

in the series can be admitted.

(16) OATMAN (2 cases)

(17) ROGALSKI (1 case)

(18) SPILLER (2 cases)

(19) STARGARDT (10 cases)

Zeitschr. f. Augenheilk, 1913, XXX. p. 95.

Also Arch. f. Ophth. 1909, lxxi, 543.

(20) VOGT. (6 cases)

Monatschr. f. Psych. u. Neur. 1905, XVIII, 163.

(21) WANDLESS. (3 cases)

(22) WOLFSOHN. (1 case)

(23) DR. LEONARD FINDLAY'S three cases which form the subject of this thesis.

The above make a total of 67 cases.

Sydney Stephenson (in the discussion at the end of Mayou's paper, Trans. Ophth. Soc. U.K. 1904, XXIV, p.145) states that he had a case of a girl aged 12 years. It is also mentioned that Still and Gunn had shown cases at a previous meeting but I have been unable to find an account of them in the Trans. of the Ophth. Society.

Spielmeyer's four cases are doubtful because of the possibility of syphilis being an etiological factor.

In addition there are the following cases which I have not verified personally:-

Hirschberg, 1 case, quoted by Oatman.

Pusey,	5 cases	)
Jennings,	3 -	)
Feingold,	3 -	) cited by **Clark.**
Lutz.	4 -	)
Stirling,	3 -	)
Dercum.		)
Turner.		) cited by Wolfsohn.

From a digest of the clinical histories in the above-mentioned list of juvenile cases, I have attempted to find connecting links with regard to the three dissenting factors:

I. Age incidence.

II. Race proclivity.

III. Eye Symptoms.

I. Connecting links in regard to age incidence.

The onset of the disease in by far the greater number of infantile cases is in the third to the sixth month. Thereafter a gap exists until the period of second dentition is reached when one meets with a group of maculo-cerebral juvenile cases. Careful search has, however, revealed quite a number of straggling cases in which the symptoms of the disease commenced between the period of infancy and second dentition. One of rarest times of onset is perhaps between the ages of 1 and 2 years. The cases which form the subject-matter of this thesis fill this gap. As far as I am aware they are the youngest juvenile cases in which a pathological examination

has been made. In the matter of age incidence, therefore, they very closely resemble infantile Tay Sachs' disease.

To illustrate how the intervening gap between infancy and second dentition may be filled up, I append the following table. More examples may easily be discovered to conform to some of the years mentioned.

Infancy.

↑

Period of onset of disease.	Cases.
Just after the 1st year.	Dr. Findlay's three cases described in this thesis.
During the 2nd year.	The third child in Vogt's second family. *
During the 3rd year.	F. E. Batten's 5 cases (1914).
During the 4th vear.	Bielschowsky's 4 cases.
During the 5th year.	Ichikawa's case.
During the 6th year.	Firükowa's 2 cases.
During the 7th year.	Mayou's three cases (1904)

↓

2nd Dentition.

* Vogt reported six cases out of three families, viz: 2 in the first, 1 in the 2nd, and 3 in the third. As Gifford points out, however, - "The second of these families is most interesting as showing a tendency towards the Tay-Sachs type (i.e. infantile). The child seen by Vogt showed the first signs of the disease at 4 years and died three years later. But there were two other children in the family who evidently had the same disease; one of these began to fail at 4 years and died two years later: while in a third child the disease began in the 2nd year and developed so rapidly that blindness and death occurred in the third year."

After the age of 2nd dentition, there is a large group of cases (the "macular" group) about the ages of 12-14 years - the period of puberty.

It is natural, I think, that the "grouping" of the cases should be at the periods of infancy, 2nd dentition, and puberty. Peculiar bio-chemical changes take place at these times and if a breakdown in the nervous system is imminent, the probability is that it will occur then, rather than in the intervening latent periods.

We have the authority of Mott* that very "important synthetic chemical changes take place 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.

Conclusions.

1. The difference in age incidence between the infantile and juvenile forms of Tay-Sachs' disease should not be regarded as a sufficient reason for the complete separation of the two types.
2. Dr. Findlay's cases, the subject of this thesis, in the matter of age incidence, are very closely related to the infantile form of Tay-Sachs' disease.

* Proc. Roy. Soc. Med. March 1911, p.175.

II. Connecting links in regard to race proclivity.

Sachs, in his article in Osler & McCrae's "System of Medicine"* makes the following observation:- "The infantile form invariably occurs among the Hebrews and among them only." His statement must necessarily carry the greatest weight. The number of reported cases of infantile Tay Sachs' disease has, however, greatly increased and now I think it would be more correct to make this statement:- "The large majority (but not all) of the cases of infantile Tay Sachs' occur among Jews." Again, regarding the juvenile type, one may state that the majority (but not all) are Gentiles.

I give the following data as showing the inter-relationship in the matter of racial proclivity between the infantile and juvenile types.

(1) There are some published cases of Infantile Tay Sachs' disease in NON-Jewish children.

(a) Cockayne reports the case of a child, healthy till 5 months, who showed characteristic macular changes. The child was of English descent. Cockayne does not actually use the term "Gentile" but from other remarks in his paper, he evidently means the reader to infer that the child was not a Jew.

* 1910, Vol. VII, p. 873.

(b) Gifford makes the following remarks in an excellent and original article.

"While a large majority of the cases of Tay-Sachs' (he always uses this term in referring to the infantile type) occur among Jews, it is by no means confined to that race. Besides a number of cases among Aryan Gentiles, at least one case has been reported among the Japanese."

(c) E. M. Tarr has published an article entitled, "A case of amaurotic family idiocy of non-Jewish parentage" in the Louisville Month. J. M. & S.*

(2) There are cases of Juvenile Tay Sachs' disease in children who are not Gentiles, but who, in fact, are definitely stated to be Jews.

(a) The family reported by Higier in the Deutsche Zeit. f. Nervenheilk (N.B. XXXI p.231) is exceptionally interesting. They are stated to be Jews and yet the first three are in every respect Juvenile cases, while the fourth shows Infantile eye symptoms.

1st child: Sight began to fail in the first year, simple optic nerve atrophy.

2nd child: Practically same as the first child.

* 1915-16, XXII, 353-357. This reference was obtained in the "Index Medicus" 1916. I have not been able to verify the article personally. Although most authors nowadays use the term "Amaurotic family idiocy" to mean an "infantile" case there is a possibility that this case may be a juvenile one. It being the rule, rather than the exception, for Juvenile cases to be non-Jewish, I do not think Tarr would have framed his title as he has done if he were referring to a juvenile case.

3rd child, initial symptoms not till 4th year. Motor power of limbs impaired, mild imbecility, amblyopia, nystagmus of indefinite type, atrophy of optic nerves.

4th child, was first seen when 13 months old. Pupils equal and react to light, eyeballs divergent, no paresis of muscles of eyeball, no nystagmus, sight appears to be confined to light perception only, definite atrophy of both papillae without inflammatory signs. In the region of the macula lutea there was a fairly large oval white spot with a reddish spot in the centre.

(b) Higier also reports another family (in Deutsche Zeit. f. Nervenheilk IX p.1). They are four sisters, and being normal until the ages of 12, 10, 9 and 7 years respectively may be considered juvenile cases, I cannot find any statement in the text that the patients are Jews but the name "Abramson" is suggestive, also the physiognomies portrayed in the photographs.

(c) Gordon reports two cases, a brother and sister, aged 13 and 9 years respectively. They are stated to be offsprings of Russian Hebrews.

Intermarriage between Jews and Gentiles, has been suggested as a reason for the occurrence of Tay Sachs' disease in Gentiles, while the predilection for Jews is said to be an illustration of the general observation that nervous

degenerations are more prone to occur in Jews than other races.

Conclusions.

1. The difference in race proclivity is not a sufficient reason for the complete segregation of the infantile and juvenile types of Tay Sachs' disease.

2. Cases are reported of infantile Tay Sachs' disease occurring, not in Jews, but in Gentiles.

3. There are reported cases of juvenile Tay Sachs' disease occurring, not in Gentiles, but in Jews.

III. Connecting links between the infantile and juvenile types of Tay Sachs' disease in regard to eye symptoms.

No difficulty is experienced with regard to such conditions as nystagmus and optic nerve atrophy. There are numerous examples of each in both types of Tay Sachs' disease. Nystagmus is not a rare occurrence and Coriat mentions it specially in his article entitled "Some new symptoms in Amaurotic Family Idiocy." Our interest, therefore, centres round the peculiar phenomenon of the "cherry-red" spot at the macula lutea. This is usually situated in the middle of a whitish-grey oval patch about twice the size of the optic disc. The long axis of the oval is horizontal and its edges are softened. Waren-Tay

thought the appearance was somewhat similar to that seen in embolism of the central artery of the retina. A few remarks as to the cause of the ophthalmoscopic appearances will be made later under the section dealing with the pathology of the retina. From the clinical standpoint, however, I have noticed that there is a certain amount of variation in regard to what I might term the "setting" of the "cherry-red" spot. By this I mean that certain descriptions convey the idea that the zone round the "cherry-red" spot was very white. Other cases are described as having a yellowish ring round the spot, others a whitish-grey. As mentioned later there are published accounts of cases of juvenile Tay Sachs' disease in which one finds descriptions of reddish spots at the macula lutea in the centre of a greyish-white area (vide Wolfsohn's case); red spot without any surrounding white zone (e.g. Ichikawa's case); reddish spot enclosed in a pigmented part of darker colour (one of Mülberger's cases). These macular appearances in such juvenile cases have received scanty attention. True there are very few juvenile cases with macular red spots, but apart from that, they would be disqualified as not conforming exactly to the pathognomonic infantile picture. A pigment ring round the red spot instead of a white ring would seem to be a sufficient excuse for disqualification. I am not competent to discuss this fully but it would seem that there is a possibility that the appearances at the macula are not as stationary as might be imagined. In this connection the infantile case reported by Dr. Mary Buchannan*

* Schumway & Buchannan, American J. of Med.Sce., N.S. CXXIX p.35.

is instructive. When first seen, it is reported that "Directly in the macular region of each eye there was a horizontally oval, white area, in the centre of which was a sharply defined cherry-red spot. The white area measured about two discs' diameter across, and faded off gradually into the surrounding retina.....Later examinations made by Dr. Buchannan showed a gradual reduction in the size of the white spot, which took the shape of a vertical instead of a horizontal oval, and became greyish in colour, while the red spot assumed a brown hue. The lesion did not disappear entirely." Child died aged $2\frac{5}{12}$ years.

Is it not possible that if such an infantile case had lived longer, the macular lesions might have disappeared completely? By far the greater number of infantile cases die before the age of 2 years. If we had more reports of cases living over 2 years we might find more varied ophthalmoscopic reports. Be that as it may, Buchannan's infantile case shows that the macular appearances may change from time to time. Similarly it is at least a possibility that a juvenile case with a pigmented ring round the red spot might at one time be discovered to have a white ring. Wolfsohn's juvenile case showed a macular orownish-red spot in a greyish-white area and no other abnormal retinal changes, and must therefore have borne a very close resemblance to the infantile type.

Again, one could hardly expect the pathological process in Tay Sachs' disease to manifest itself in

juvenile cases in exactly the same way as it does in an infant. In the juvenile cases the disease is slow and chronic, in infantile, sharp and acute. Might not such a very intense degenerative process as one finds in the infantile form account for the "cherry-red" spot? Might not the same degenerative process, very much modified in intensity, produce no "cherry-red" spot in the juvenile cases? Below, Weber's case is given as an example of an infantile type without any "cherry red" spot and it is interesting to note that the following remark is made, viz:- "The disease has been a very CHRONIC one." Again, in the first family described by Higier, it is the fourth and youngest child who has the red spot at the maculae - the three older children have no macular changes.

The following cases are given as connecting links between the infantile and juvenile groups in regard to the macular changes.

(1) A case is reported of infantile Tay Sachs' disease with no pathognomonic "cherry-red" spot at the macula.

Parker Weber has reported the case of a female child, a Jew. The onset of the initial symptoms was at 3 months and the disease was a very chronic one. This case is therefore definitely "infantile" both in the matter of age incidence and racial proclivity. The familial element was also present, as two other members of the family appear to have died of the disease. The clinical symptoms were suggestive

e.g. inability to sit up at 14 months, muscular weakness, "head-lolling", apathy, inability to grasp properly, variable amount of rigidity, nystagmus, blindness &c. The important point, however, is that the ophthalmoscopic examination at 14 months by Drs. Gruber and Markus revealed "No pallor of macular region with a "cherry-red spot". In spite of this Weber states that the case was almost certainly one of family amaurotic idiocy. There was a possibility of associated internal hydrocephalus. At 14 months the circumference of the head was 18½ inches.* It may, however, be remarked that Coriat specially mentions hydrocephalus in his article "Some new symptoms in Amaurotic Family Idiocy".

(2) <u>There are reported cases of juvenile Tay Sachs' disease</u> with red spots at the macula.

(1) <u>Wolfsohn's Case</u>.

"In the region of each macula there was a greyish-white area in which was seen a small brownish-red spot." Bilateral optic nerve atrophy. No other retinal changes elsewhere.

(2) <u>Mülberger's case I</u>.

There was a reddish part enclosed in a pigmented portion of darker colour.

* Holt, "Diseases of Infancy & Childhood", 1917, p.20, gives the average circumference of head at 18 months in a normal child as:- male 18½"; female 18".

(3) Ichikawa's Case.

Dark red spot and no white zone.

(4) Gordon's Case. (Case 2. "Pearl F.")

There was an oval area including the fovea and of about the size of the papilla much redder than the remainder of fundus."

(5) F. E. Batten (1903) Case "R.B."

"At each macula there was a reddish black spot" .....the region immediately surrounding the dark spot was paler than the rest of the fundus and more atrophic looking."

(6) R. D. Batten (1897)

In both eyes of Harry S., "at the macula there is a dark pear shaped patch of a red colour dotted over with fine points of retinal pigment."

(7) Higier (the family described in Deutsche Zeit. f. Nervenheilk XXXI p.231, 4th child). In the youngest or fourth child there was a fairly large oval white spot with a reddish spot in the centre in the macular region.

(8) Rogalski's case.

The bright red oval spot at the macula was surrounded by a pigmented ring.

(9) Kuffler's cases.

The first and third children had reddish spots at the maculae.

(3) <u>There are families in which some members had macular</u> symptoms somewhat resembling the infantile type while other members of the family, having no reddish spot, might be said to resemble the juvenile type.

(1) <u>Higier's 2nd family</u> (the one described in Deutsche Zeit. f. Nervenheilk XXXI p. 231).
The first three children had no "red spots", but this was present in the fourth!

(2) <u>Kuffler's family</u>.
The first and third children had reddish spots at the maculae, but not in the other two members also affected with the disease.

<u>Conclusions in regard to the discussion on eye symptoms.</u>

I. In the published reports of infantile and juvenile Tay Sachs' disease it is possible to find connecting links with regard to the eye symptoms.

2. Nystagmus and optic nerve atrophy are present in both types of the disease.

3. The appearance of the pale-coloured zone and the "cherry-spot", in infantile cases may change and so come to resemble more closely certain juvenile cases.

4. A pigmented instead of a white ring round the red spot should not be emphasised as a strong disqualifying factor.

5. The tendency has been to lay stress upon the differences rather than upon the resemblances of the eye symptoms but the same pathological process cannot be expected to

to manifest itself ophthalmoscopically in infancy and adolescence in exactly the same way. - all the more so when in one type the degenerative process is very acute and in the other very chronic.

6. A true infantile case is reported in which there was no pathognomonic "cherry-red" spot at the macula lutea.
7. Some juvenile cases of Tay Sachs' have red spots at the maculae.
8. There are some families with juvenile Tay Sachs in which there is a mixture of types - some members of the family having macular red spots while the other members affected in the family had no such changes.

PART IV.

PATHOLOGY.

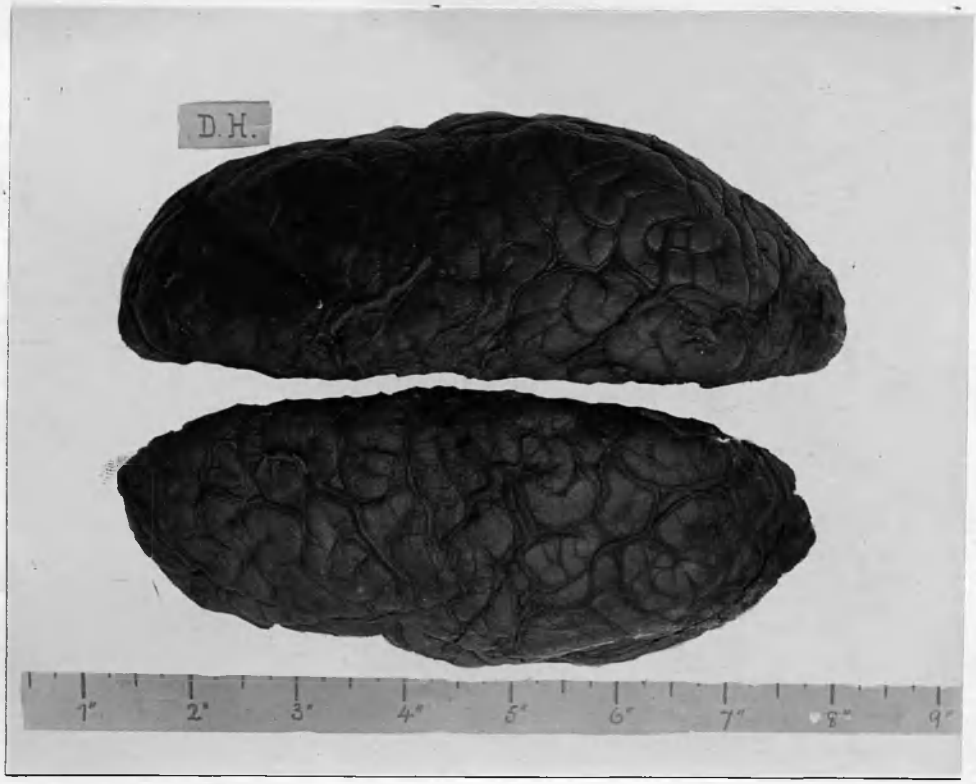


Fig. 1. (Case I.)

View of vertex of cerebrum showing appearance of the vessels + convolutions. There was marked sinus thrombosis of the longitudinal + lateral sinuses + a recent haemorrhage extending over the right frontal lobe.

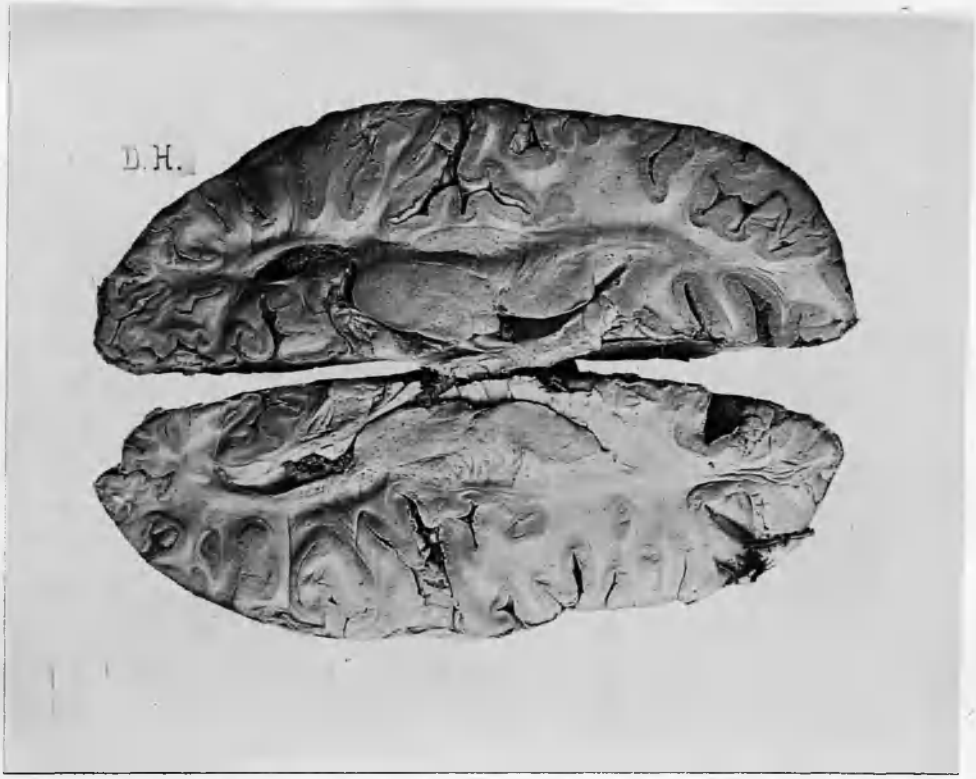


Fig 2. Case I.

Horizontal section through cerebrum showing the basal nuclei + internal capsule. No striking abnormality was observed. The grey matter, however, was unusually dark + it was thin especially at the extremities of the occipital lobes.

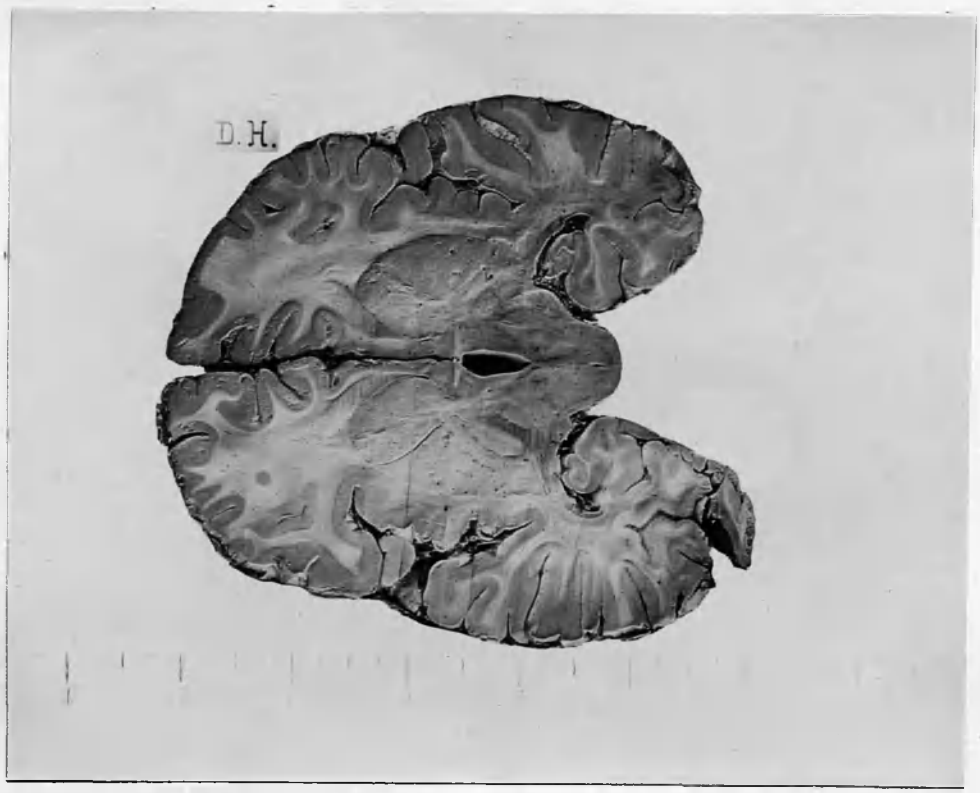


Fig. 3. (Case I.)

Horizontal section through the basal portion of the cerebrum. At the occipital poles the substance of the brain was much firmer than natural + the grey matter unusually dark + thin.

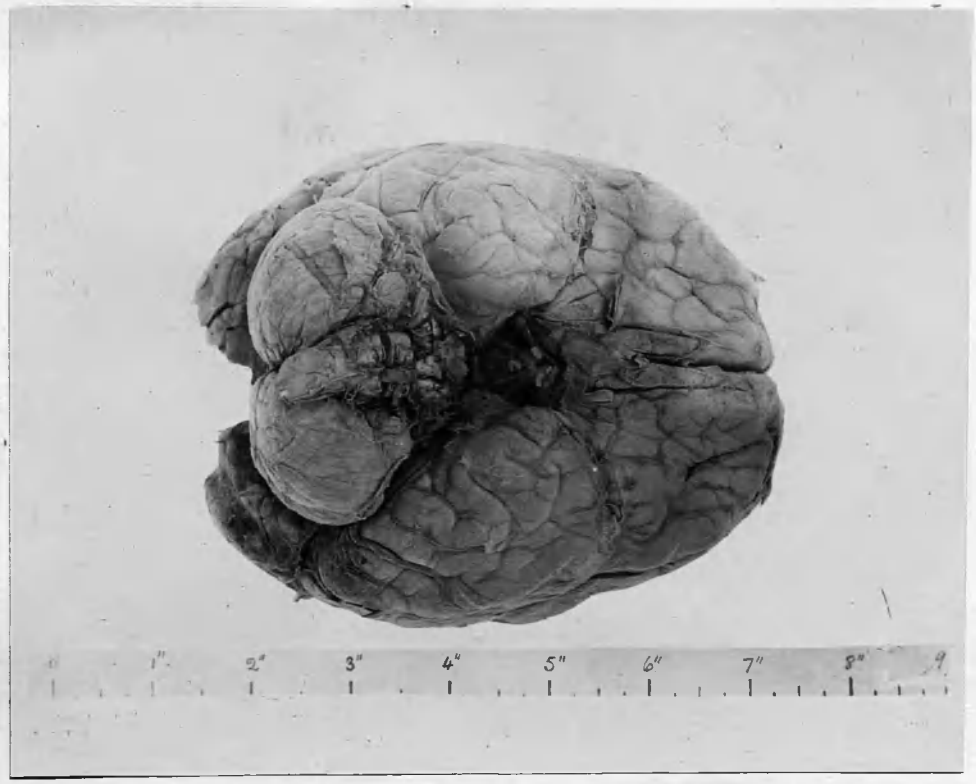


Fig. 4. (Case I.)

View of base of cerebrum + cerebellum. The remarkable atrophy of the cerebellum is well seen. A considerable part of the occipital region is left uncovered. It is interesting to compare this photograph with the "control" case fig. 15.

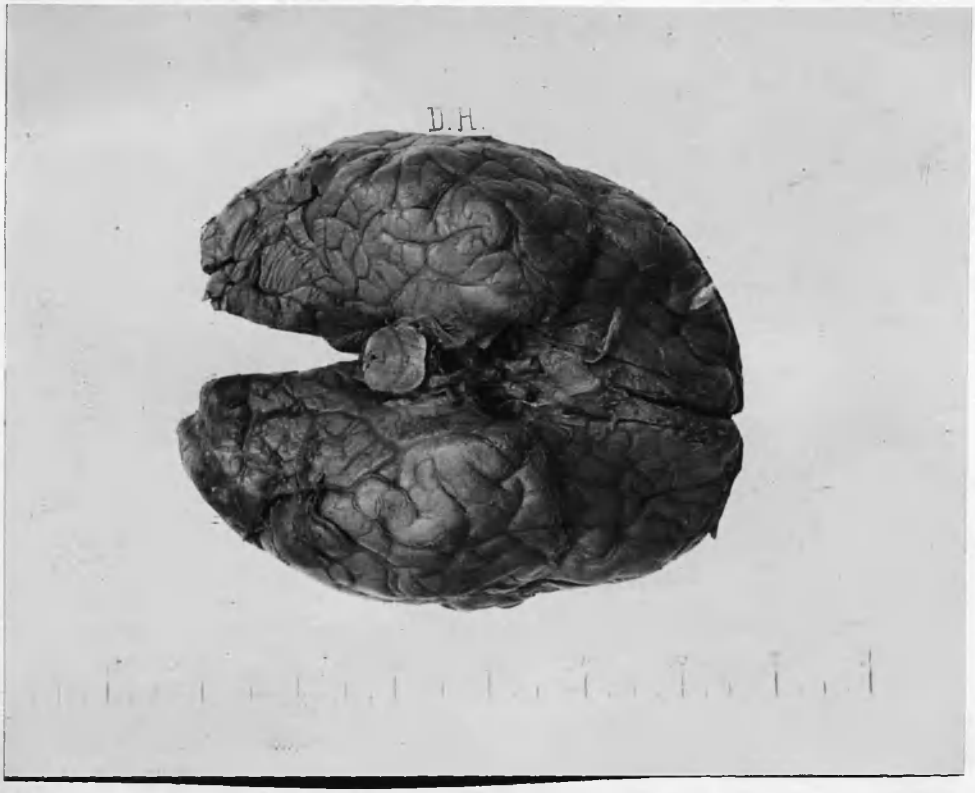
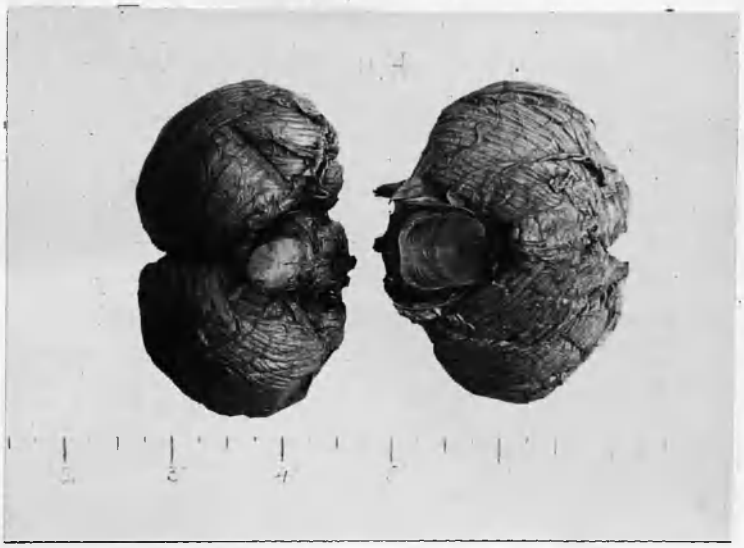


Fig 5. (Case I)

View of base of cerebrum after removal of the cerebellum. Some of the convolutions at the occipital region appear to be narrower than normal. On palpation they felt firmer than the surrounding parts.

Fig. 6. (Case I)



The cerebellum has been cut in two + the superior + inferior surfaces are shown with their remarkably narrow laminae.

Fig 7. (Case I.)

Horizontal sections through the cerebellum with medulla + pons attached. The cerebellar folia are distinctly atrophied. There is a diminution in the amount of white matter.

POST-MORTEM REPORT ON CASE I. ("D.H.")

The body was that of an extremely emaciated boy. (aged $4\frac{4}{12}$ yrs.)

THORAX:-

Heart: There was some dilatation of the right ventricle but otherwise the heart and pericardium were normal.

Lungs: Broncho-pneumonic patches were present in both the lower lobes, in the middle lobe, and in the lower part of the upper lobe of the right lung. The other parts were emphysematous.

Thymus: Very small.

Thyroid: Looked normal in size.

ABDOMEN:-

Liver showed cloudy swelling.

Kidneys also showed cloudy swelling.

Suprarenals looked normal.

Spleen was normal in size with somewhat full pulp very dark in colour.

Intestines and Stomach appeared to be normal. In the mesentery there was a large soft gland (about the size of a walnut) containing caseous matter.

Testicles and cord normal in size and situation.

BRAIN:-

Membranes: There was marked sinus thrombosis of the longitudinal and lateral sinuses. Both the hemispheres had a congested appearance and there was a recent

haemorrhage extending over the right frontal lobe.

Cerebrum:- On palpation rather firm areas were found in the right motor area, above the Sylvian fissure, and also at the tips of both occipital lobes. After making a section through those areas, nothing special was found. The grey matter was unusually dark and it was thin especially at the extremities of the occipital lobes.

Cerebellum was very small and markedly thin on palpation.

Pineal gland looked normal.

Fig. 8.
(Case II)

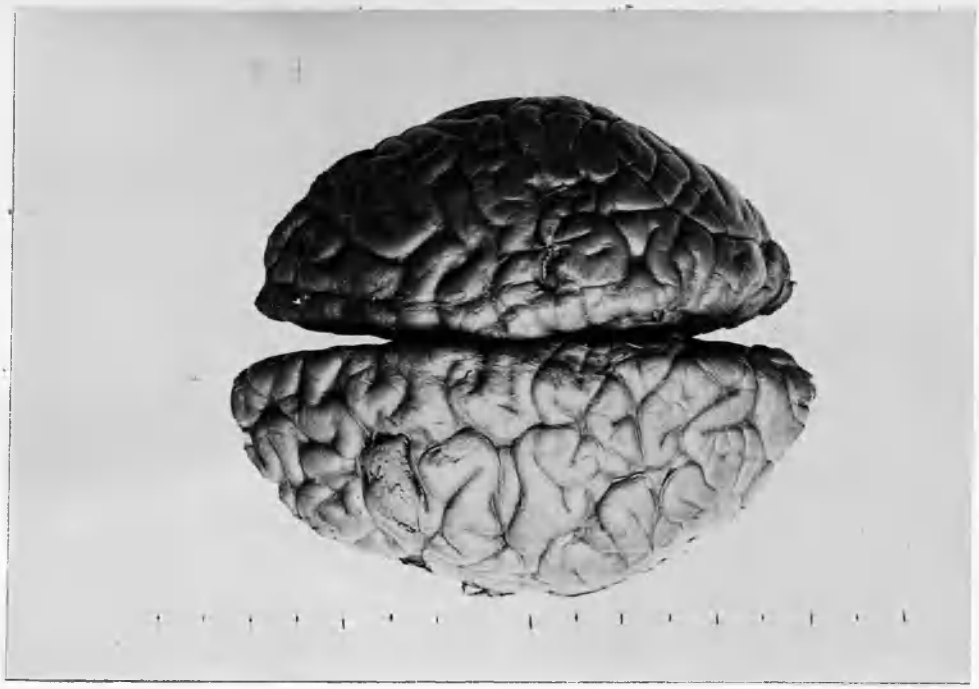


Fig. 9.
(Control Case.)

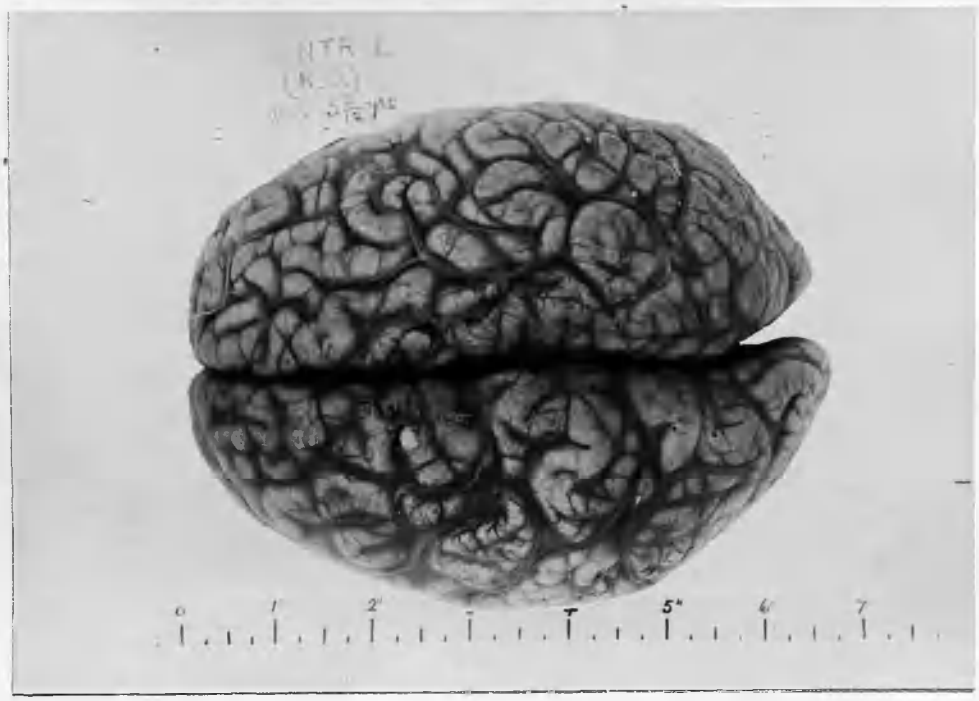


Fig 8. Case II. View of vertex of cerebrum showing that there was no abnormal fissuration. The convolutional pattern is complex but there is a general atrophy of the whole brain.

Fig. 9. Normal control, obtained from child of exactly the same age as Case II. For comparison with fig. 8.

Fig. 10.
(Case II.)

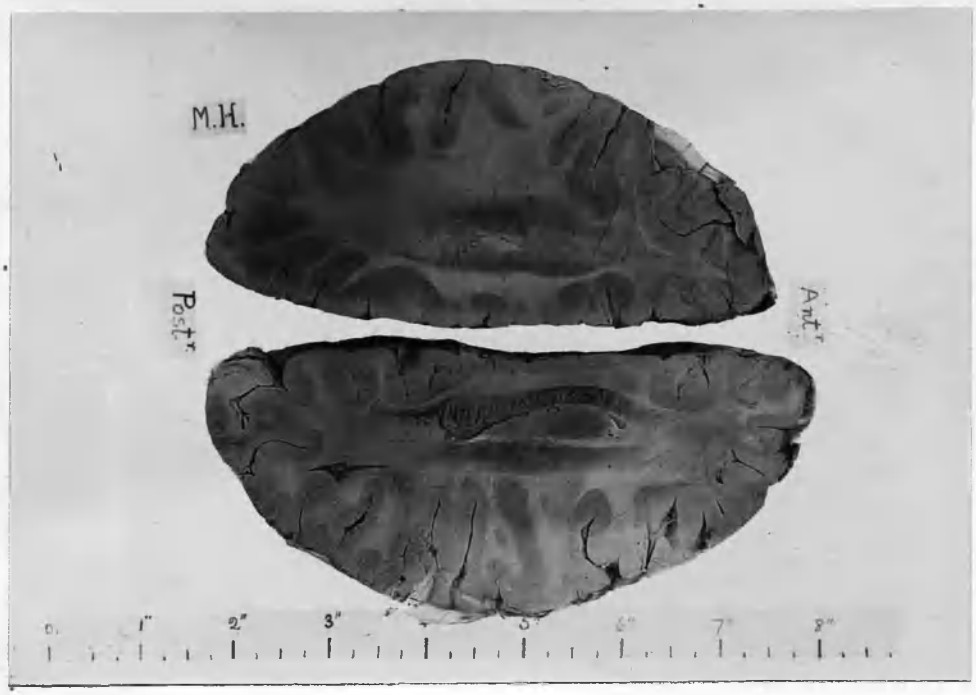


Fig. 11.
(Normal Control.)

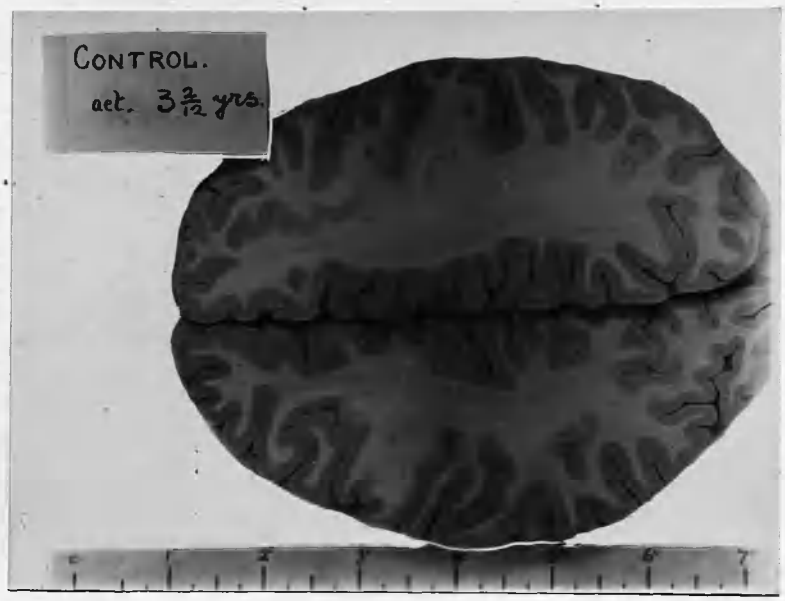


Fig. 10. (Case II.) H.S. of cerebrum showing the blurring of the junction line between the grey + the white matter.

Fig. 11. Normal control, for comparison with the above. The section through this brain is at a slightly higher level as the white matter of the centrum ovale minus is exposed. Both photographs were taken with panchromatic plates in order that the colour contrast between the grey + white matter might be faithfully reproduced.

Fig. 12.
(Case II)

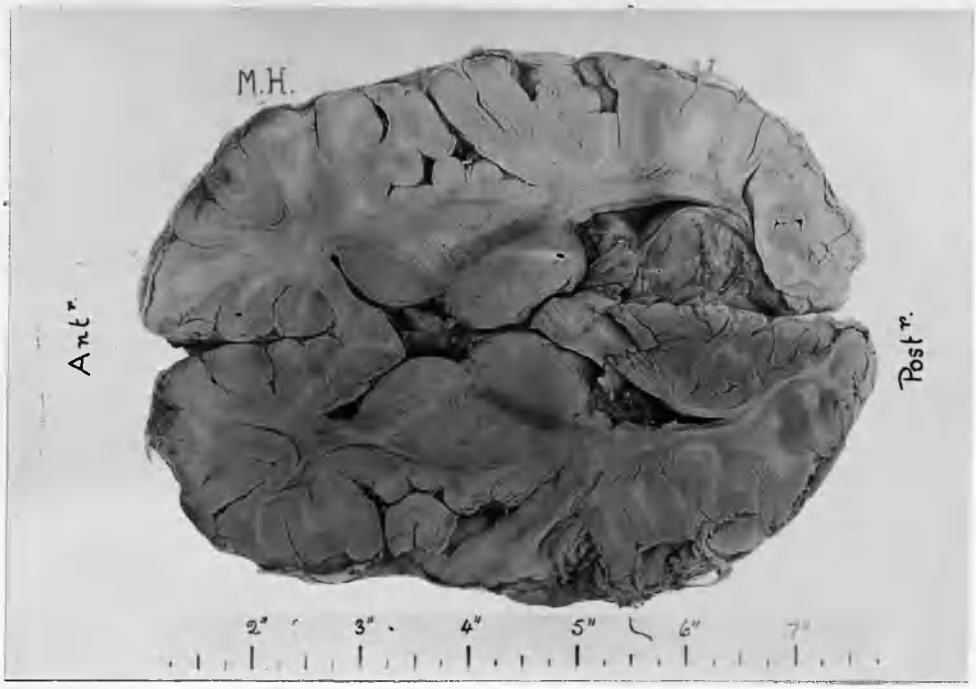


Fig 13.
(Normal control.)

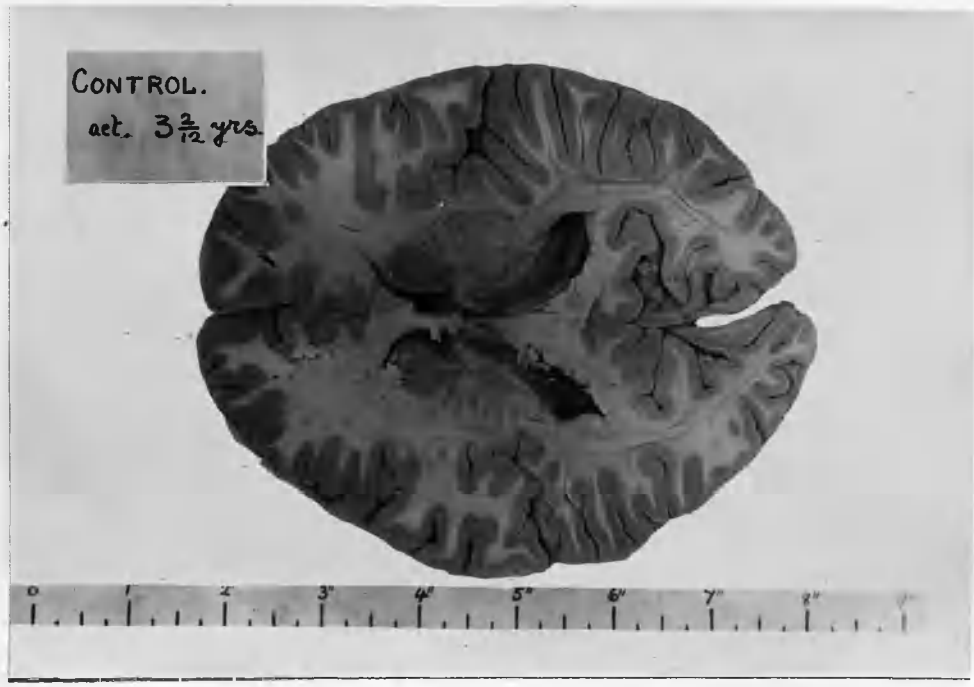


Fig. 12. H.S. through the brain of Case II. The right lenticular nucleus is small + is encroached upon by the white matter of the internal capsule.

Fig 13. H.S. through normal brain showing the marked distinction between grey + white matter. cf. fig. 12.

Fig 20.
(Case II)

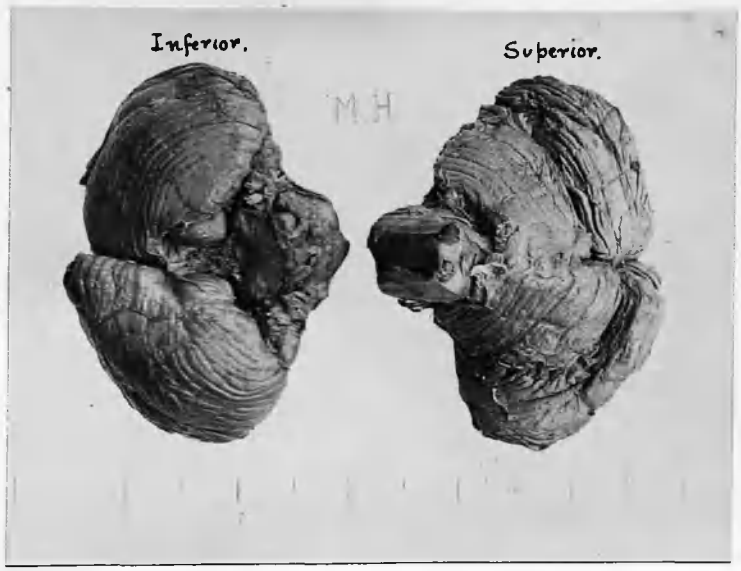


Fig. 20. (Case II.) View of superior + inferior surfaces of the cerebellum showing the thin narrow laminae.

Fig. 21.
(Case II)

Fig. 21. (Case II). Horizontal sections through the cerebellum. The pons + the medulla share in the general atrophy. The arbor vitae is shrunken + its branches widely separated from one another.

Fig. 18.

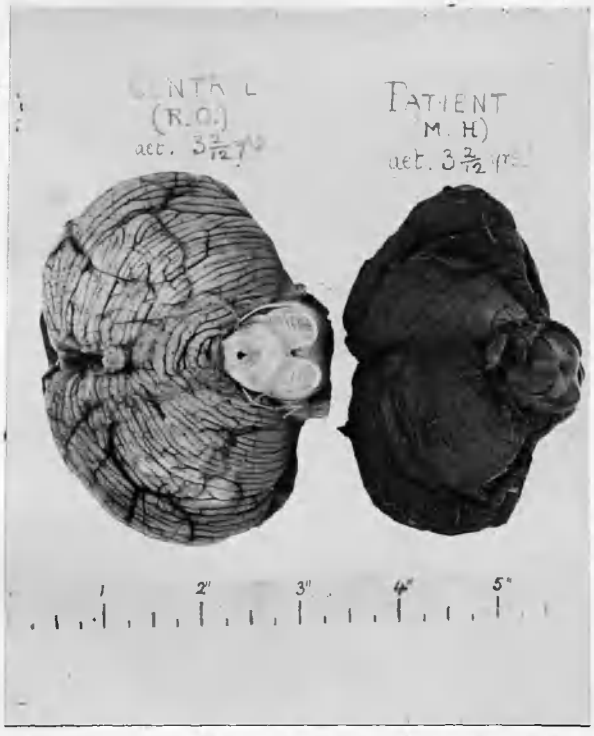


Fig. 18. Views of superior surface of cerebellum from Case II compared with normal control case. Patients age = Control's age. Both specimens were photographed side by side on the same plate — the disproportion in size is very apparent.

Fig. 19.

Fig. 19. Cut surface of the cerebellum from Case II compared with that of normal control case of exactly the same age. Note the definite atrophy of the whole substance + the wasted + thinned appearance of the arbor vitae branches. The pons is also diminished in size + it is distorted by pathological markings.

Fig. 16.
(Case II)

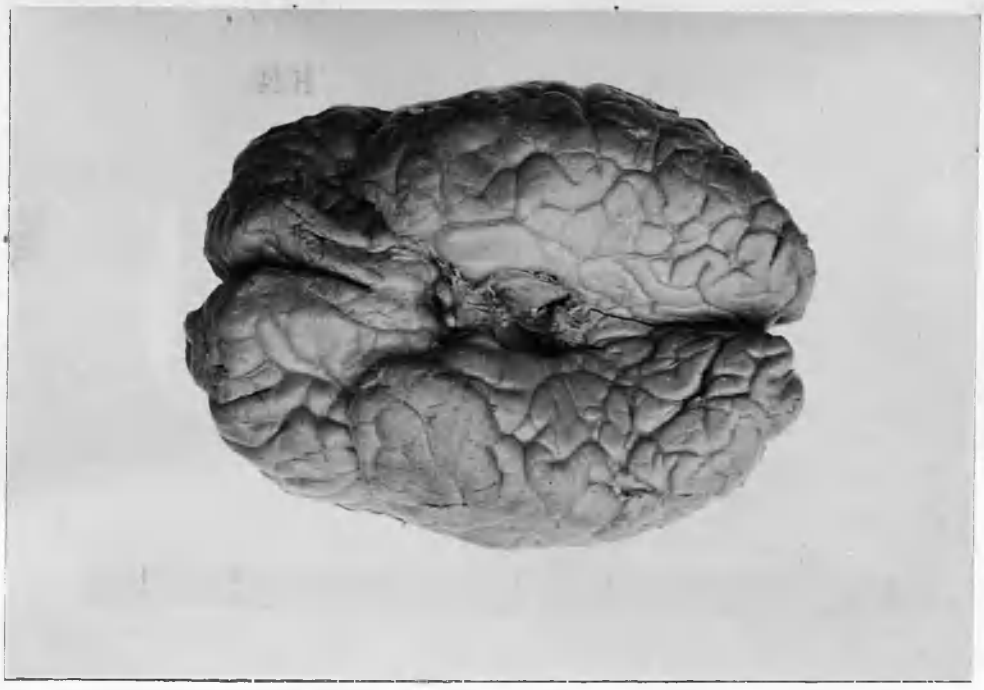


Fig 17.
Case
normal.

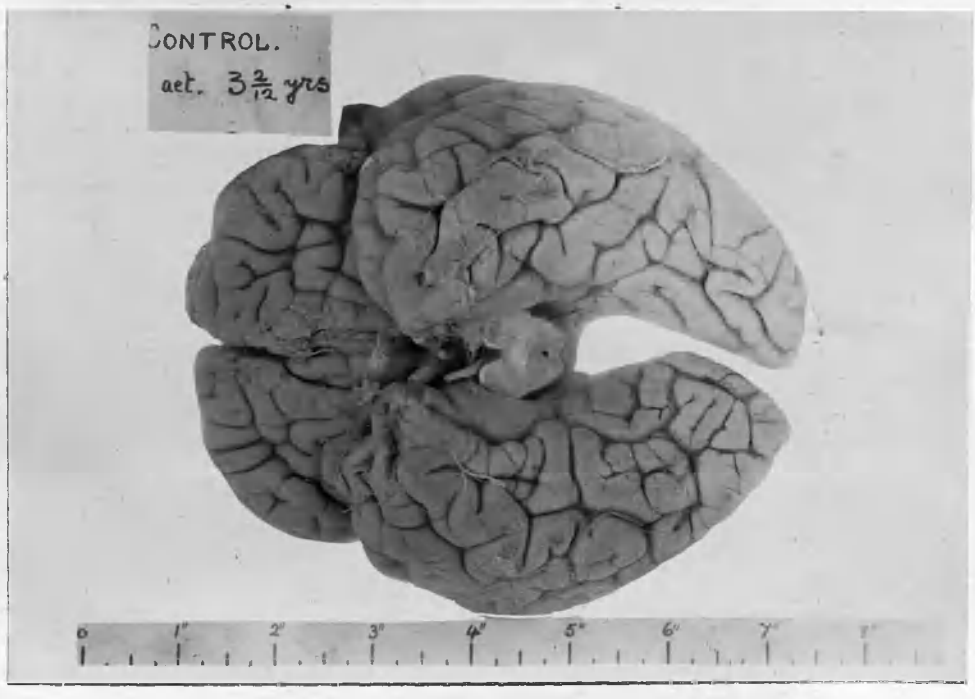


Fig. 16. Base of cerebrum after removal of cerebellum.
Case II.

Fig 17. Base of normal control - same age as above.
The convolutions are much thicker.

Fig 14.
(Case II)

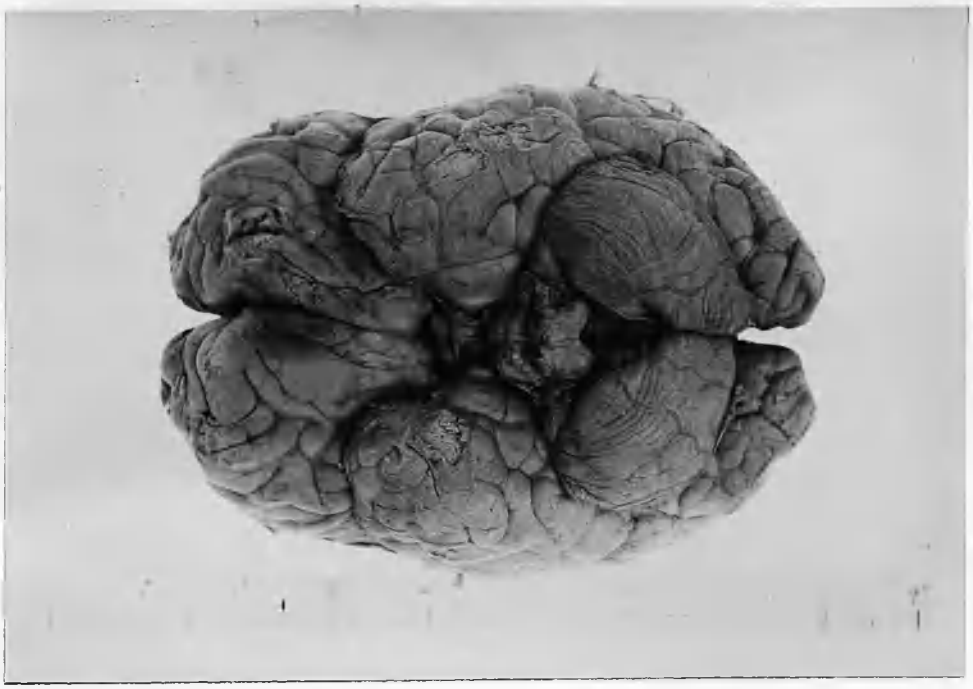


Fig 15.
(Control)

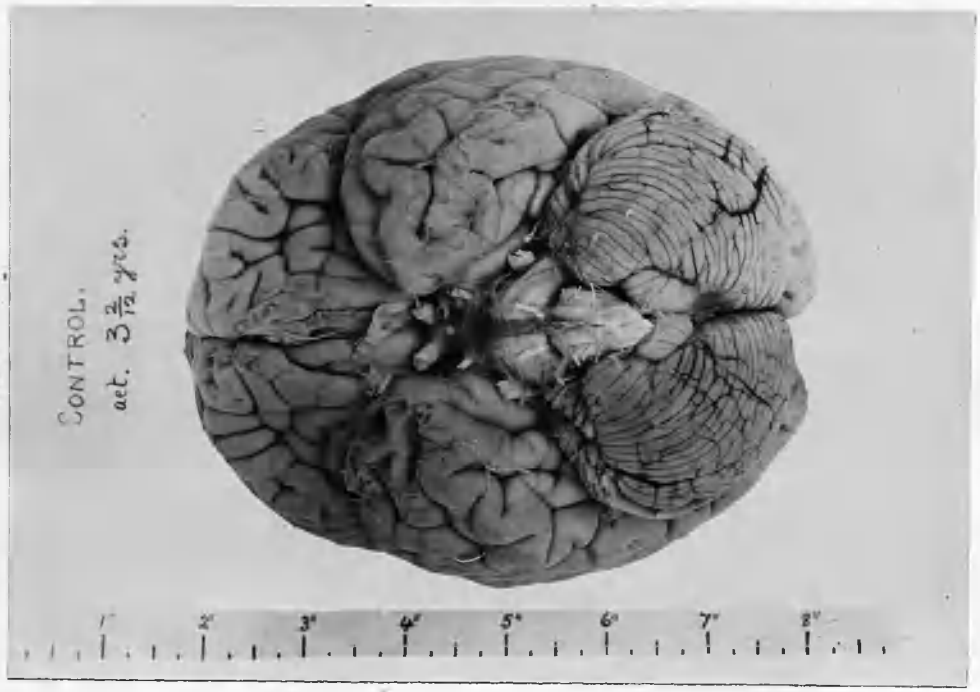


Fig 14. (Case II) Base of cerebrum + cerebellum. There is a definite atrophy of the whole substance of the cerebellum. It is small, absolutely (i.e. per se) + also relatively (i.e. compared with the cerebrum) The "weight-index" of cerebellum + pons + medulla to the cerebrum was 1:13. (Normal 1:8)

Fig 15. Brain from normal case exactly the same age as Case II. Here the cerebellum reaches almost to the tips of the occipital poles. The weight-index was normal, 1: 8:: cerebellum + pons + medulla : cerebrum.

POST-MORTEM REPORT ON CASE II. (Patient "M.H.")

The examination was conducted by Dr. Haswell Wilson, Pathologist to the Royal Sick Children's Hospital, and I am much indebted to him for the following report.

The body is that of a female child, much emaciated, aet. $3\frac{2}{12}$ yrs.

THORAX:-

The thymus has practically disappeared.

The pericardial sac is normal, and the heart, which weighs $1\frac{1}{2}$ oz., is pale and flabby. No lesion can be found in its valves or cavities. The heart muscle is somewhat fatty.

A small amount of serous fluid is found in each pleura.

The lungs are much congested and in both there is extensive broncho-pneumonic consolidation, most marked at the left base.

Pneumococci and minute gram negative bacilli of influenzal type are found in the smaller bronchi, and pneumococci alone in the consolidated patches.

ABDOMEN:-

The peritoneum is normal. The liver, weight 12 ozs., shows some small areas of fatty degeneration, but is otherwise normal. The spleen, $\frac{1}{2}$ oz. in weight, is small and the pulp is somewhat soft. The kidneys each weight $1\frac{1}{4}$ ozs. Apart from slight cloudy swelling, they are healthy in appearance. The suprarenals and pancreas show no abnormality. No lesion found in the stomach or intestines.

HEAD:-

The brain weighs 2 lbs. 6 ozs., and is distinctly atrophied, the sulci on the convex aspect being wide and gaping, and the convolutions distinctly wasted. The brain substance as a whole is soft and oedematous, but at the upper end of the Rolandic areas, especially on the left side, the substance is distinctly indurated. The distinction between the white and grey matter at the cortex is blurred in many places, especially in the motor areas. The right lenticular nucleus is small and is encroached on by the white matter of the internal capsule. Both optic thalami show whitish patches suggestive of neuroglial overgrowth.

The convolutions of the cerebellum are thin and the sulci deep. It is much harder than normal and this is associated with a definite atrophy of the whole substance. The posterior mesial fissure is very wide and deep and the cerebellum is retracted from the roof of the 4th ventricle. The convolutions of the arbor vitae are wasted and separated by wide sulci.

The pons and medulla are diminished in size, atrophied and tough and on section the markings are seen to be much distorted by whitish tissue, apparently neuroglial overgrowth. The olivary bodies stand out prominently from the medulla.

The spinal cord is very attenuated and is increased in consistence, especially in the cervical and lumbar enlargements. On section it is seen to be irregularly

congested and the grey matter is very ill defined from the white matter throughout its whole course.

Fig. 22.

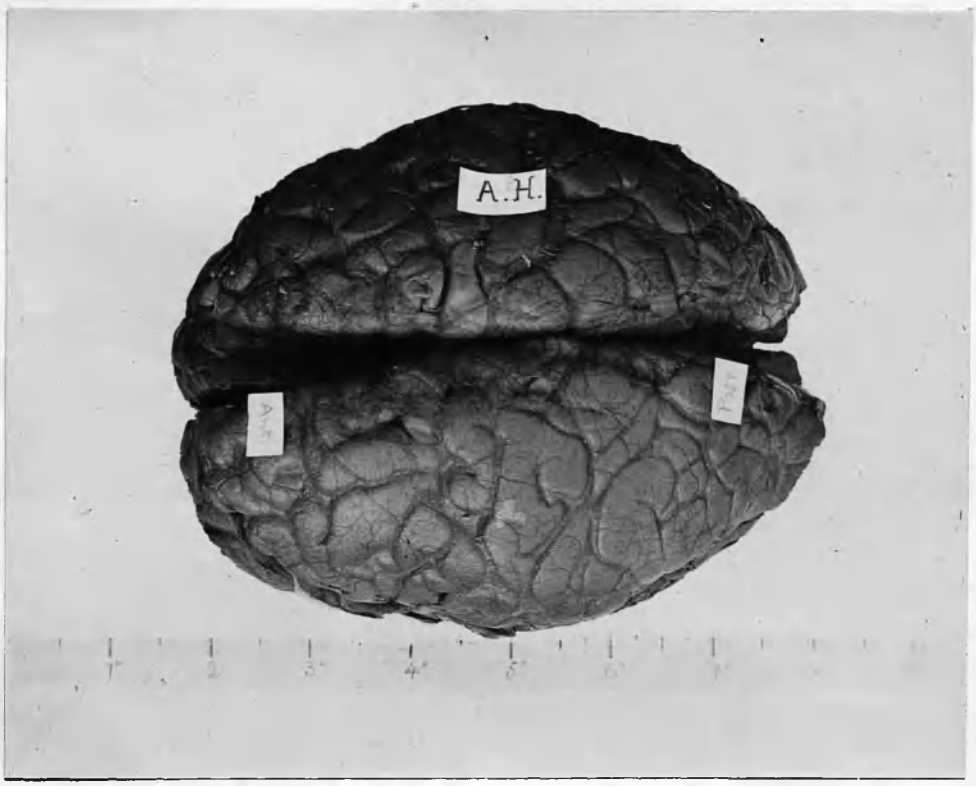


Fig. 22. (Case III)

Vertex of cerebral hemispheres. No abnormality is seen in the membranes covering the brain. The convolutional pattern is normal as far as it is possible to judge but there is some atrophy of the gyri here + there + a consequent widening of the otherwise normal sulci.

Fig. 23.

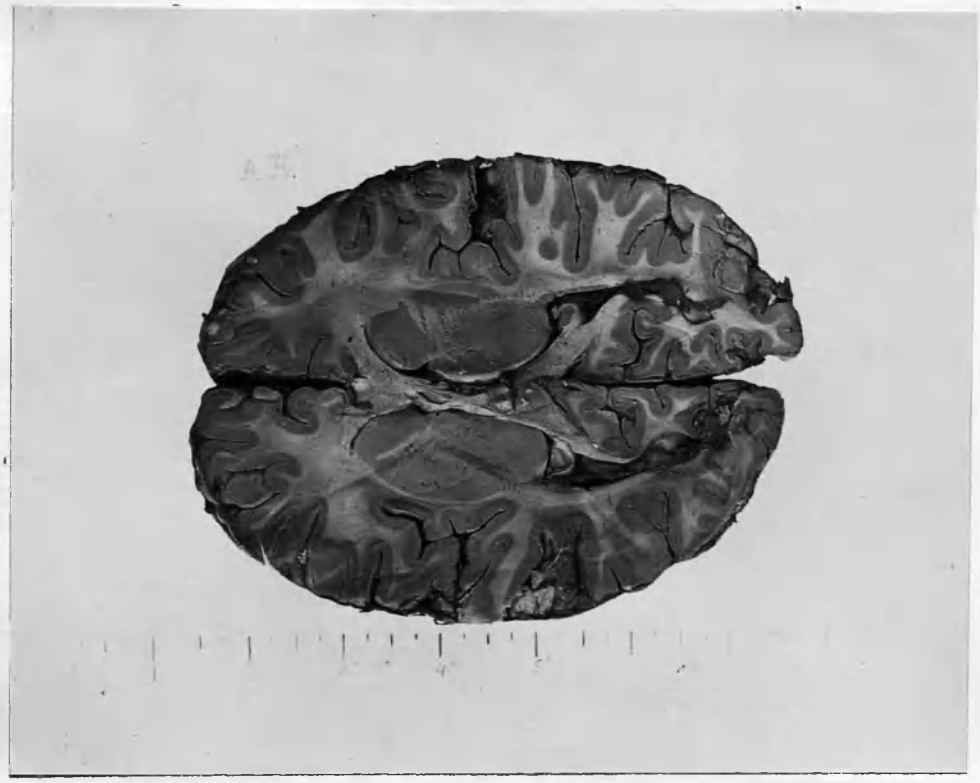


Fig. 23. (Case III) Horizontal section of cerebrum cutting through the basal nuclei & internal capsule. No gross lesion is evident.

Fig. 24.

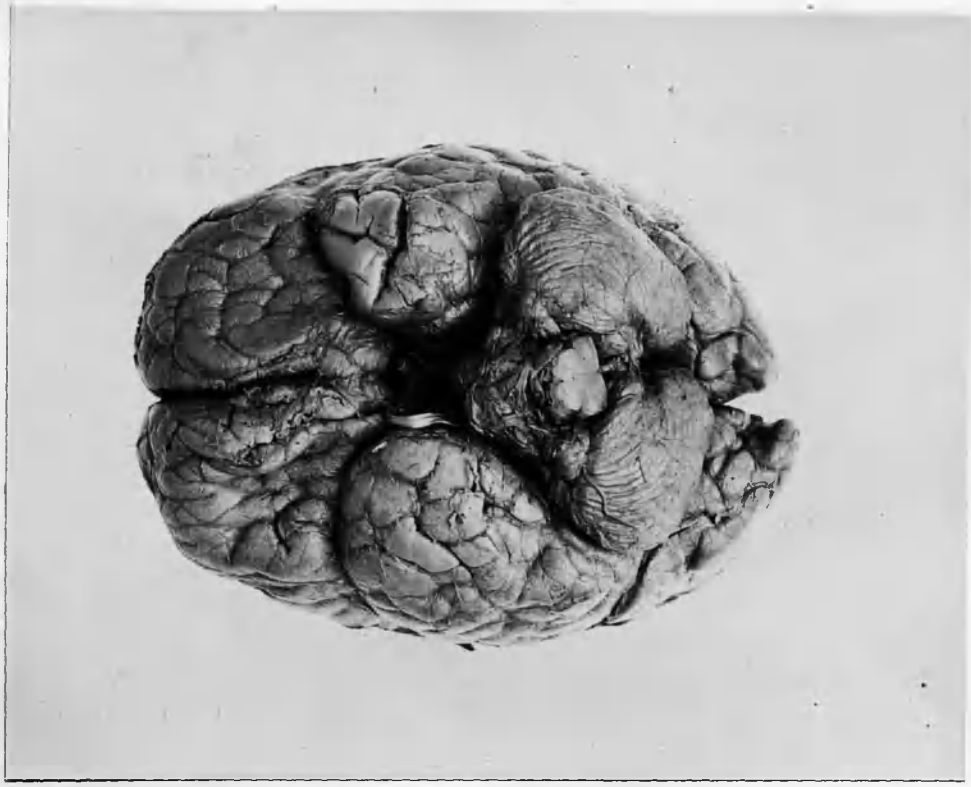


Fig. 24. (Case III.) Base of Brain.
The cerebellum is markedly diminished in size as in the other 2 cases. The optic nerves are thin.

(For comparison of normal brain + cerebellum with this case vide fig. 15.)

(Fig. 25.)

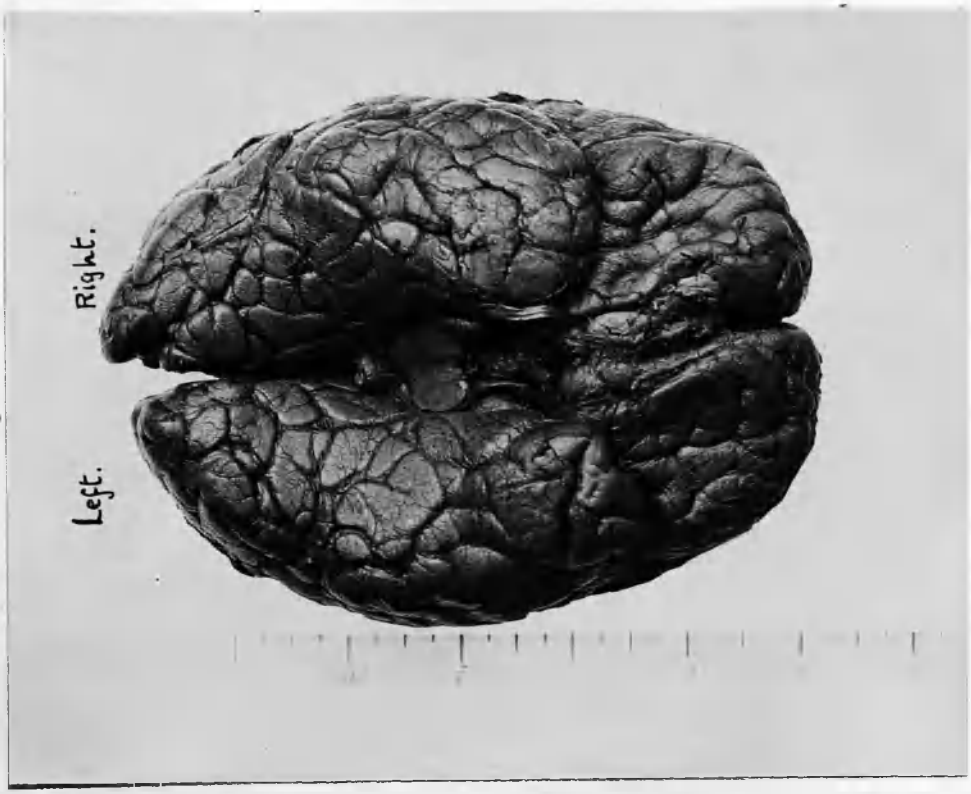


Fig. 25. (Case III) View of Base of Cerebrum after removal of the cerebellum. The substance of the brain was extremely dense at the posterior part of the left occipital pole + this photograph shows an inequality in size as compared with the right pole.

Fig. 26.

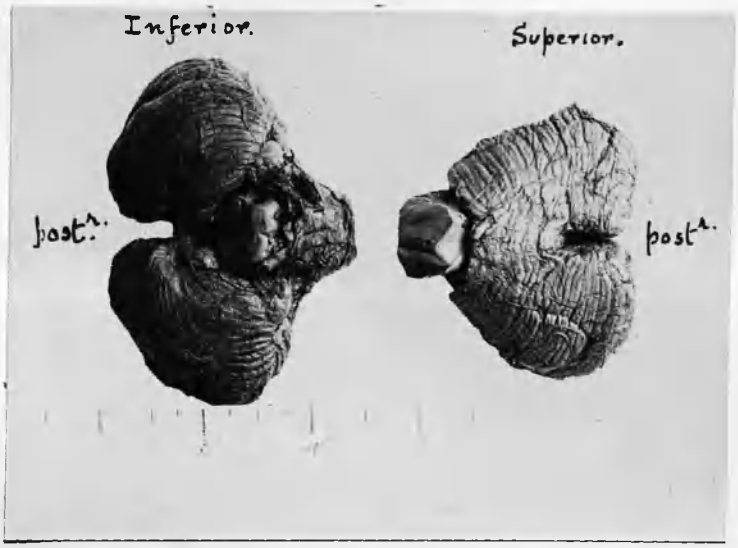


Fig. 26. (Case III.) The superior + inferior surfaces of the cerebellum. Note the shrunken diminished size of the hemispheres, + the narrow laminae. The posterior median fissure is very wide + gaping.

Fig. 27.

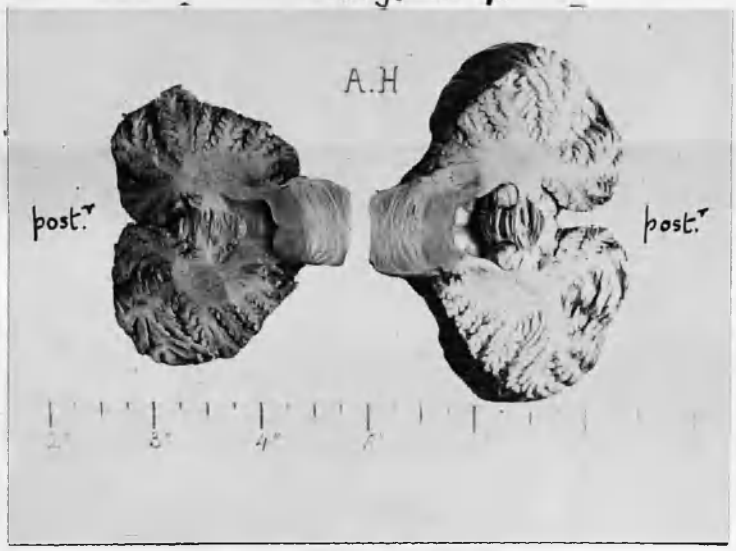


Fig. 27. (Case III.) View of the cut surfaces of the cerebellum after making a horizontal section through it. The branches of the arbor vitae are shrunken + are widely separated from one another.

POST-MORTEM REPORT ON CASE III (Patient "A.H.")

The examination was conducted by Dr. Haswell Wilson.

"The child's body is fairly well-nourished but very anaemic in appearance. (age $2\frac{5}{12}$ years).

Double broncho-pneumonia is present with scattered areas of consolidation occurring throughout each lung. The bronchi contain abundant muco-pus. No disease found in any of the other organs.

HEAD.

No excess of cerebro-spinal fluid is present and no abnormality is seen in the membranes. The substance of the brain is extremely dense and the convolutions are somewhat atrophied so that the sulci are wide and gaping. This condition is specially marked in the posterior part of the left occipital lobe.

The cerebellum is markedly diminished in size and the arbor vitae is much shrunken and the branchings widely separated from one another. The medulla is also smaller than normal. No gross lesion is evident in the substance of the brain other than the increase in consistence. The optic nerves are very thin and hard."

Summary of Post-Mortem Reports.

An account has been given of three autopsies which were conducted 27 to 32 hours after death.

The ages of the children, all members of one family, were respectively $4\frac{4}{12}$, $3\frac{2}{12}$, and $2\frac{5}{12}$ years at death. The eldest was a male; the others females. Emaciation was present to an extreme degree in the first (or eldest) child, to a less extent in the second, while the body of the third, or youngest, was well nourished.

THORAX:-

In each case the lungs were congested, and showed extensive scattered areas of broncho-pneumonic consolidation. The other contents of the thoracic cavity may be considered negative.

ABDOMEN:-

With the exception of some cloudy swelling and small areas of fatty degeneration in some organs, also a walnut-sized mesenteric gland in Case I., nothing abnormal was found in this abdominal cavity.

HEAD:-

(a) Membranes, Sinuses, and Vessels:- Sinus thrombosis and a recent superficial haemorrhage was observed in Case I, otherwise nothing abnormal was detected.

(b) Cerebro-Spinal Fluid:- No excess of fluid present.

(c) Cerebrum:- In each case the convolutional pattern showed no abnormality with regard to its complexity and arrangement. The gyri, however, in Cases II and III were shrunken and wasted, while the intervening sulci were correspondingly wide and gaping. Palpation of the cortex revealed firm indurated portions at the Rolandic areas, and occipital poles. Gross horizontal sections of the cortex revealed nothing of importance except unusually dark and thin grey matter at the occipital poles in Case I, and some blurring of the grey and white junction line at the motor areas in Case II.

(d) Basal Nuclei:- Right lenticular nucleus (in Case II) was small and encroached upon by the white matter of the internal capsule, while the optic thalami showed some whitish streaks. Otherwise, examination was negative.

(e) Cerebellum:- A very definite atrophy of the whole substance of this part of the brain was apparent in each case. The laminae were thin and wasted, the sulci deep, and in some places wide, while the branchings of the arbor vitae were shrunken and widely separated from one another.

(f) The Pons, Medulla, Spinal Cord and Optic Nerves were diminished in size.

Discussion.

I. Summary of P.M. findings in the Infantile Type of Tay Sachs' disease.

II. Summary of P.M. findings in Juvenile Type of Tay Sachs' disease.

III. Comparison of the present cases with the above.

I. Summary of P.M. findings in Infantile Type of Tay Sachs' Disease.

The number of clinical accounts of this disease is numerous as compared with the published descriptions of autopsies. This is no doubt due to the difficulty in obtaining permission for a necropsy from the Jewish race. Nevertheless, from the accounts of Sachs, Kingdon and Risien Russel, Mott, Poynton, Parsons and Holmes, Spiller and others, a definite pathological picture may be obtained. The following is Risien Russel's resumé in Allbutt and Rolleston's System of Medicine:-

> "The cerebral and spinal meninges are usually free from any abnormal appearances, though in Sachs' first case a few slight adhesions of the former were noted. The convolutions and sulci of the brain are normally arranged: but in the case just referred to, there was some abnormal fissuration which was regarded as indicative of a brain of low development. The sulci were wide in some cases, pointing to a certain amount of atrophy of the convolutions: but this atrophy varies in

different cases. The brain has sometimes been unduly firm to the touch, especially in the frontal region. The ventricles are normal and do not contain any excess of cerebro-spinal fluid: though there may be some compensatory oedema of the meninges."

I find that nearly all the reports agree in most of the essential details as described above, and that they serve to confirm one another. Three observations may be made for later comparison:-

(1) There are no gross abnormal macroscopic appearances in the brain. Such irregularities as a confluence of the Rolandic and Sylvian fissures, a gaping of the opercula to show the Island of Reil (which led Sachs at first to describe the condition as an "agenesis corticalis" or arrested cortical development) may be taken as exceptional occurrences. Sachs* now attaches very little importance to such appearances. It is important to realise that the naked eye picture is more or less negative. Does not this term "Idiocy" in the name "Amaurotic Family Idiocy" (a synonym for the Infantile type of Tay Sachs' disease) suggest various Simian appearances? As Mott has suggested, the disease should be termed amaurotic dementia rather than amaurotic idiocy.ø

(2) Although there are no gross naked eye changes, many reports describe a slight atrophy of the cerebral convolutions.

* (Vide Sachs' article in Osler & McCrae's "System of Medicine")

ø Mott Proc. Royal Society of Medicine. Mar. 1911. Vol. IV Pathological Sect. p.173.

(3) I have been much struck by the fact that portions of the brain substance are frequently described as having an increased consistency - e.g. Poynton Parsons & Holmes describe the brain in their 1st case as "unnaturally firm, and of the consistence of gutta percha.....and it offered resistance to the knife in cutting it." Again Mott states "The substance of the brain in the frontal, central and temporal regions is much firmer in consistence than natural.....and feels like leather or india rubber covering a softer substance within."
(4) Attention has generally been focussed upon the cerebrum, and as many reports do not make definite statements about the cerebellum at all, one may justifiably assume that macroscopically it was practically normal.

From the above digest a comparison of the post-mortem findings in the cases described in this thesis with those found in the infantile type of Tay-Sachs' disease, it may be stated:-

A. The agreement lies in the possession of appearances similar to those described under headings (1), (2), and (3).
B. The difference lies in the non-compliance with observation (4) as described at greater length later.

II. Summary of P.M. Findings in the Juvenile type of Tay Sachs' Disease.

The pathological anatomy in juvenile cases of Tay Sachs' disease has been studied by Batten, Behr, Bielschowsky, Brooks, Rogalski, Spielmeyer, Spiller, Vogt, and Wolfsohn. From an examination of these reports, it is evident that the macroscopic appearances found in juvenile cases differ in no fundamental respect from those found in infantile cases. A separate description, is, therefore, unnecessary.

III. Comparison of the post-mortem appearances of the writer's cases with the infantile and juvenile types.

The parallelism of the post-mortem findings of the present cases with the infantile and juvenile cases is self-evident, with one exception, - the cerebellum. In the present cases, the cerebellum was unusually small: in the infantile and juvenile types, this is not the case. Can this difference be reconciled? Having made an extensive search through the literature upon this subject, I have found one infantile and one juvenile case reported, in which it is definitely stated that the cerebellum was unusually small, viz:-

(1) Infantile case described by Gordon Holmes.*

The cerebellar folia "were very slender and wasted, as much so indeed as I have ever seen in either primary or secondary atrophy of this organ."

* Proc. Roy. Soc. Med. March 1911. Vol. IV. Path.Sect. p. 192

Holmes remarks that from the cellular changes in the brain he was inclined at once to regard the case as an example of amaurotic family idiocy, but that certain features (among them the considerable atrophy of the cortex of the cerebellum) made him hesitate to do so. "The fact, however, that a later member of the family presented the characteristic clinical features and ocular changes, and that the same cellular affection which is pathognomonic of amaurotic family idiocy was found throughout the nervous system by Drs. Mott and Carlyll makes it imperative to include this case in the disease."

(2) Juvenile case described by Bielschowsky in article entitled "Über spät-infantile familiäre amaurotische Idiotie mit Kleinhirnsymptomen".*
From the point of view of similarity with my cases, Bielschowsky's report is illuminating, as he states definitely that the cerebellum was extremely small, not only in its absolute weight but also in its relative weight, i.e. to the cerebrum.
I may here state that in my cases the relative weight of the cerebellum, Pons and Medulla combined, to the weight of the cerebrum was about 1 to 13. Anatomical works usually state that (except in young infants) the normal index should be 1 to 8. In the "control" case, a normal index was obtained.

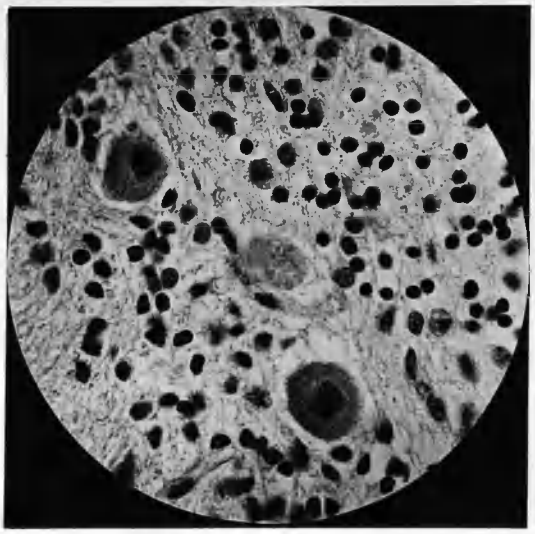
* In Deutsche Zeitsch. f. Nervenheilk 1913 1.7

The accompanying photographs which I have taken illustrate the post-mortem changes described above.

Conclusions.

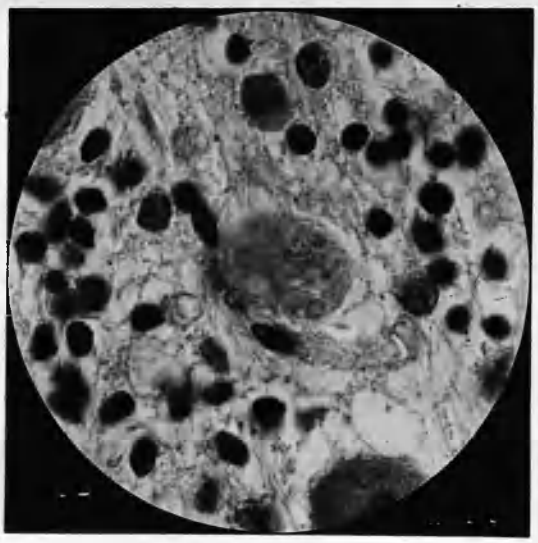
The post-mortem appearances found in the present cases closely resemble those found in infantile and juvenile Tay-Sachs' disease. The resemblances are fundamental, the differences incidental.

Fig. 28.



× 500

Fig. 29.

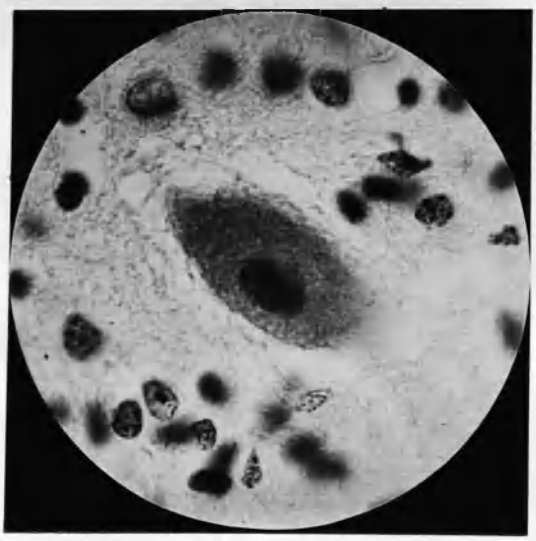


× 1,000

Fig. 28. (Case III) Three Purkinjé cells showing different stages of degeneration. They have lost their normal fusiform shape + the protoplasm is very granular. In one, the nucleus is central, in the 2nd eccentric, while the 3rd cell has no visible nucleus. [Haemalum + Eosin] × 500.

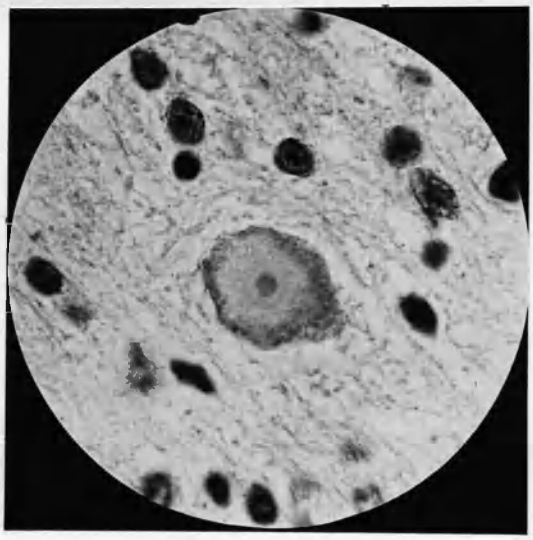
Fig. 29. (Case III) High power view of the most degenerated cell in the above figure. The protoplasm is very irregularly stained. In some cells there was an attempt at vacuolation. [Haemalum + Eosin] × 1000.

Fig. 30.



× 1,000

Fig. 31.

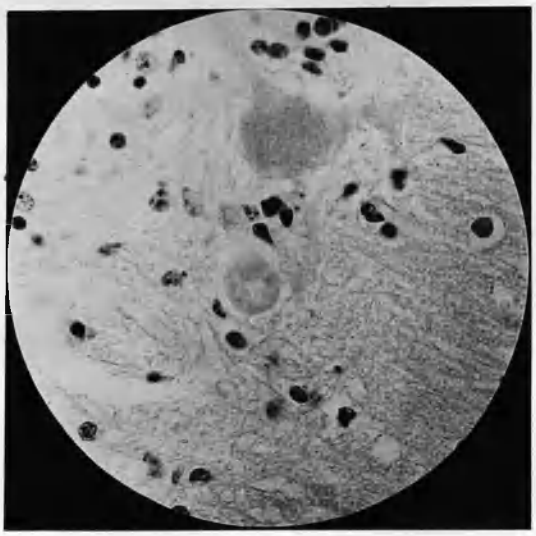


× 1,000

Figs. 30 + 31. (Case III.)

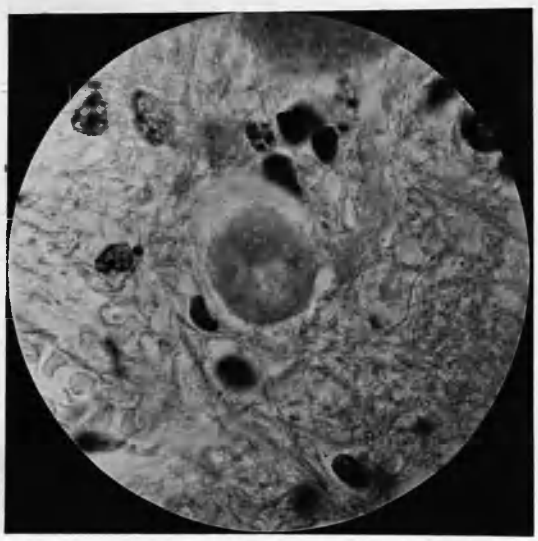
Here two other cells of Purkinjé in various stages of chromatolysis are seen. One has still a resemblance to its original pyriform shape while the other is quite globular. The nucleus is tending to become eccentric in one, in the other it has almost entirely disappeared + vacuolation of the cell is commencing. Note the large atypical granule cells. [Haemalum + Eosin]

Fig. 32.



× 500

Fig. 33.



× 1,000

Fig. 32. (Case II) Note the pale-staining "shadow" forms of the Purkinjé cells, a marked degree of chromatolysis has taken place [Harris' Haematoxylin + Eosin]

Fig. 33. H. P. of above.

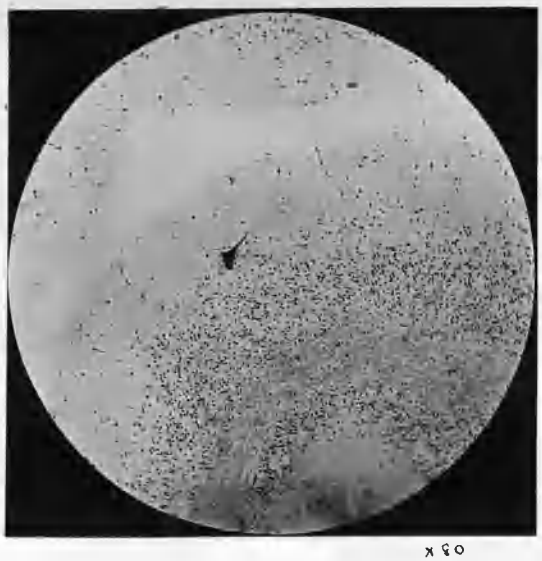


Fig. 34. (Case II)

x 80

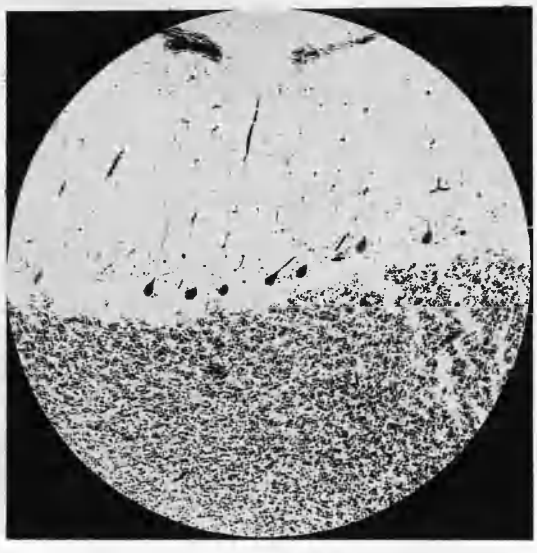


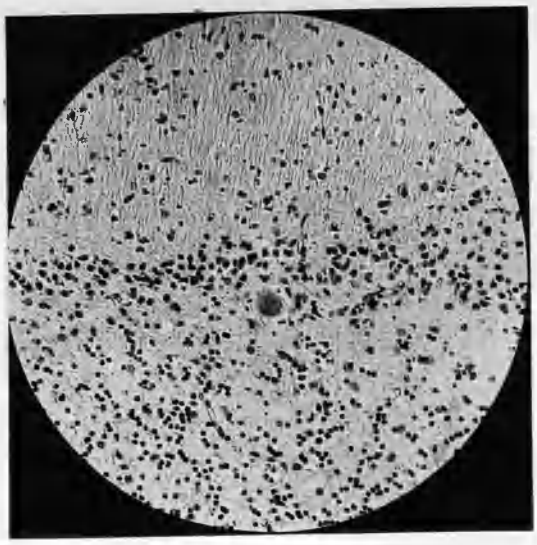
Fig. 35. ('Control')

x 80

Fig. 34. Case II. One of the best Purkinje cells which could be found is here represented. Even under this comparatively low power it is seen to be swollen. [Bielschowsky Stain]

Fig. 35. Cerebellum from normal child exactly the same age as Case II. Both were fixed + stained in the same manner. Both are taken under the same conditions photographically. Reference Purkinje cells the size, position, + number of the cells should be compared. Also the condition of the dendrites – they are thinner in the control. Note the increased thickness of the granular layer in the "control" + also the greater number of granules. greater?
[Fixed in Müller. Stained Bielschowsky.]

Fig. 36.
Case III



molecular layer.

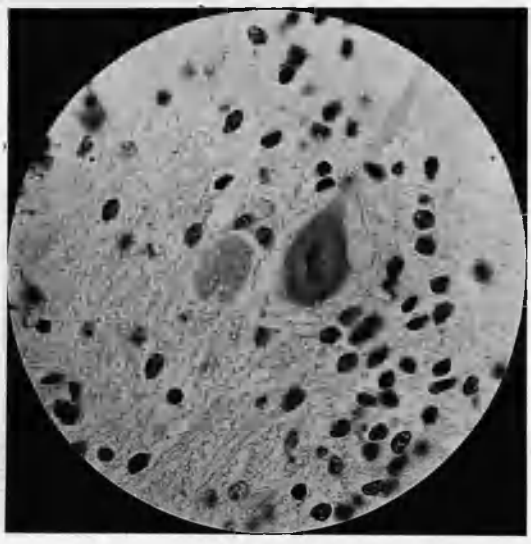
large cells.

a Purkinje cell.

Granule layer.

× 100

Fig. 37.
(Case III)

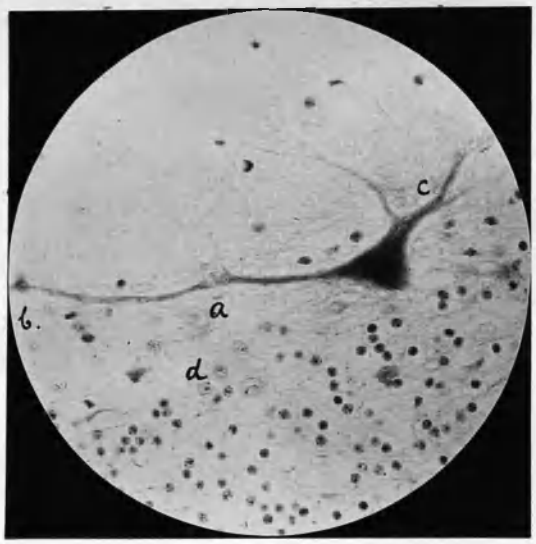


× 500

Fig 36. (Case III) a folium of the cerebellum showing the "large-cell layer" (referred to in the text as possibly large neuroglia cells "Körnschenzellen") in the region of the Purkinje cell zone. A degenerated Purkinje cell is seen. [Haemalum + Eosin]

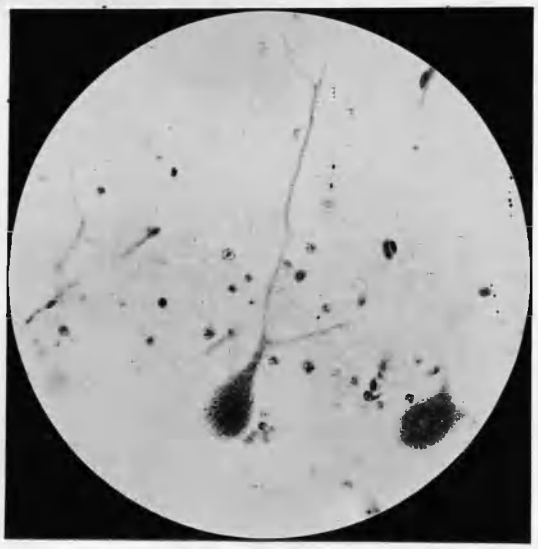
Fig. 37. (Case III) a Purkinje cell with swollen process. Also a "shadow" Purkinje cell.

Fig. 38.
(Case II)



× 500

Fig. 39.
(Control.)

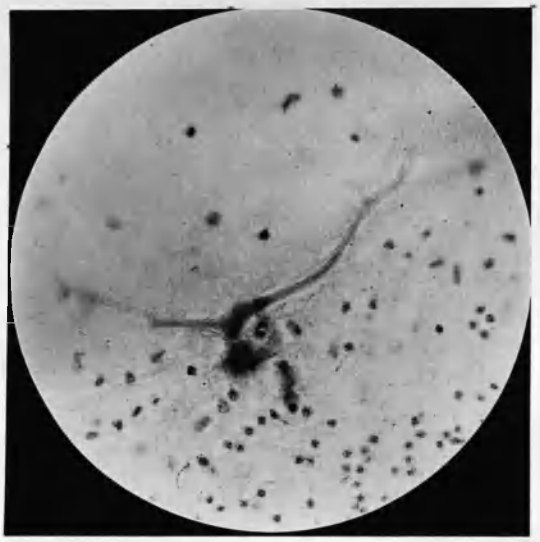


× 500

Fig. 38. (Case II) A Purkinje' cell – one of the best preserved which could be found, showing, nevertheless, degenerative changes in the protoplasm, swelling of the cell + loss of the pyriform shape + at (a') + (b) swellings on the dendrites. (a) is about 2 cells breadth distant from the body of the cell + this is said to be a favourite position for such swellings – a special feature of Tay Sachs disease. At (c) the processes are very thick. At (d) the pale stained large? granule cells may be seen.
[Fixed in Müller. Stained Bielschowsky.]

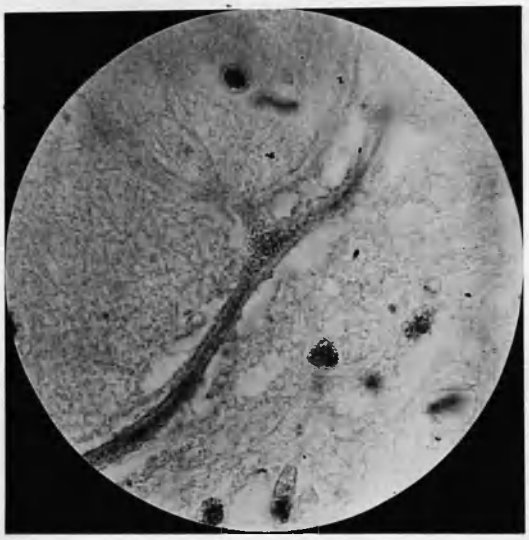
Fig. 39. Control case to compare with the above. Note the pyriform shape + compare the thickness of the dendrites.
[Fixed in Müller. Stained Bielschowsky.]

Fig. 40.



× 500

Fig 41.



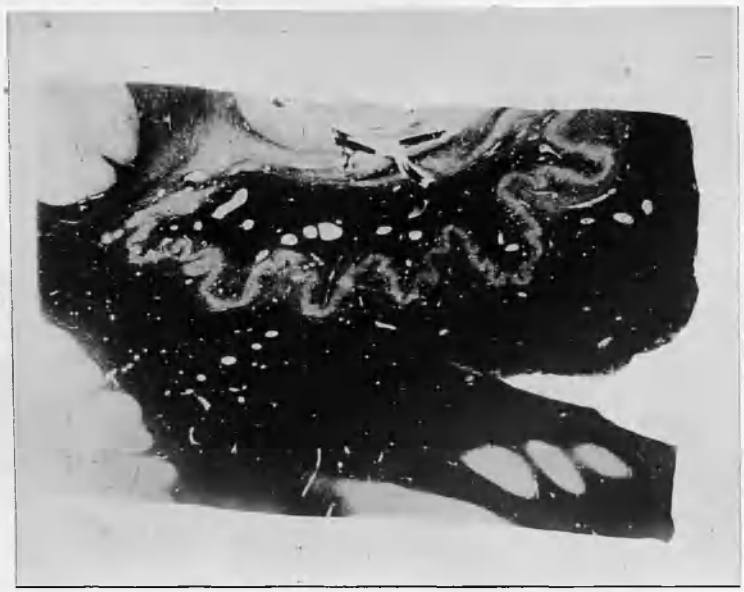
× 1,000

Figs. 40 + 41. are examples of "swelling of the dendrites" in 2 Purkinje cells. The specimens were stained by Bielschowsky's silver impregnation method.

Fig 42.

x 5

Fig 43.

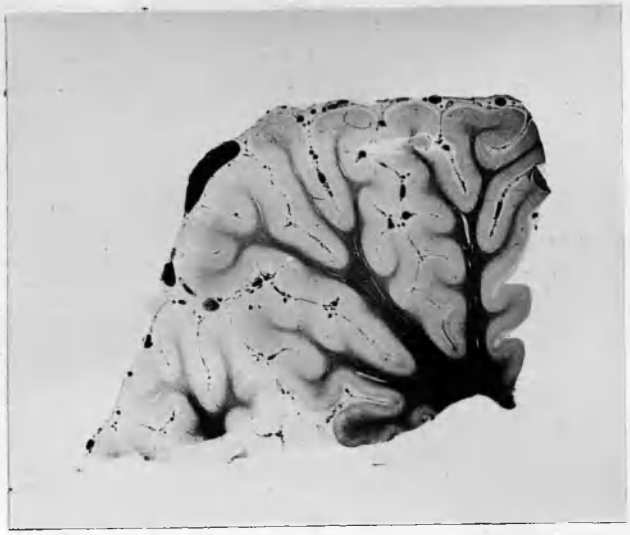


x 5

Fig. 42.
A dentate nucleus stained by the Weigert-Pal method + showing some patchy degeneration of the surrounding white matter.

Fig. 43.
Another view of a dentate nucleus stained by the Weigert-Pal myelin sheath method.

Fig. 44.



× 5

Fig. 45.

× 4.

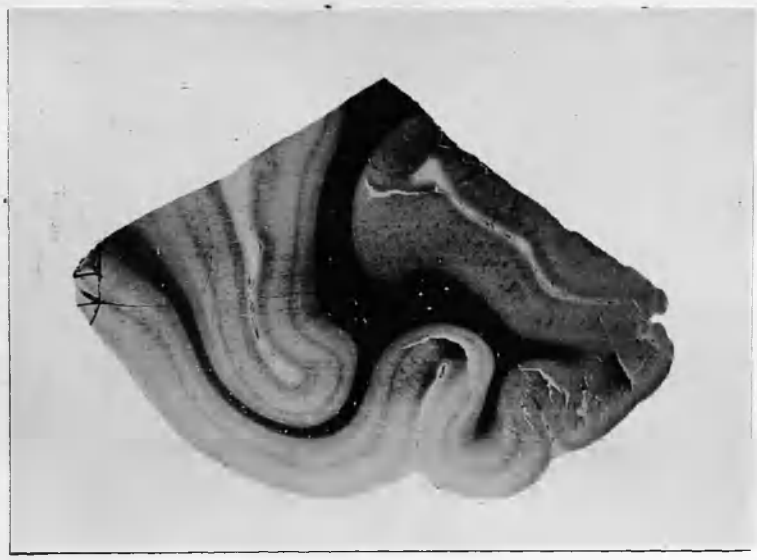
Fig. 44.
Portion of cerebellar cortex stained by Weigert-Pal. At the terminal parts of the branchings of the white matter there is some degeneration.

Fig. 45.
Another portion of cerebellar cortex stained by the ~~Weigert~~-Pal myelin sheath method.

Fig 46.
(Case III)

× 25

Fig. 47.
(Case II)



× 4.

Fig. 46. (Case III.) A low power view of a folium of the cerebellum. showing the narrow atrophied appearance. Generally there was very little white medullary substance seen. In this section there is none, but, of course, this may be due to the section having been cut in an oblique manner through the folium. Only one or two flask-shaped Purkinjé cells could be found in the whole of this lamina. The layer of large cells in the region of the Purkinjé area can be seen as a narrow band running round the folium - separated by a slight space from the ordinary "granules". Horiz. Sect. [Staind Haemalum & Eosin.]

Fig. 47. (Case II.) Horizontal section of the occipital pole slightly above the level of the calcarine fissure. Gennari's band is seen. The white medullary substance has stained quite darkly by the Weigert-Pal myelin method.

PATHOLOGICAL EXAMINATION.

I. Macroscopical examination.

The gross macroscopical appearances have already been dealt with under the section dealing with the autopsies. It only remains to be said that during the process of cutting up the brain for detailed histological examination no further abnormalities, other than those already mentioned, were found. It may be remarked, however, that one could almost guess the position of the Rolandic area by the "feel" of the knife as it cut through this portion of the brain. It will be remembered that the motor and occipital areas were firmer to the touch than the rest of the brain: confirmation of this was obtained by the knife meeting with slightly more resistance there. Nowehere, however, did I get actual "grating" with the knife as is mentioned by Sachs. With regard to the sinus thrombosis and superficial haemorrhage in Case I, there is little to relate. It was apparently of no import. It is a curious coincidence, however, that Mott* describes an almost identical haemorrhage in one of his cases of infantile Tay Sachs.

II. Method of Fixation.

After removal from the calvarium the brains were placed in Müller's Fluid. Two of the brains remained in this fluid for about 20 months, the third for about 7 months, before any histological examination was made. It is

*Mott. Archives of Neurology, 1907. III, p.237.

perhaps unfortunate that some other methods of fixation were not also attempted. The spinal cords received the same treatment.

III. Embedding Methods employed.

After the hardening in Müller's fluid, small portions of brain tissue and spinal cord were embedded in celloidin in the usual way. Since absolute alcohol softens celloidin, it had to be avoided and dehydration completed with phenol xylol. When staining for Nissl's granules, it was found that the carbolic acid interfered with the basic aniline dyes. The only alternative therefore was to remove the celloidin or make some paraffin sections. Both were done. Generally speaking with bilateral structures one part was embedded in celloidin, the other in paraffin. Numerous artefacts, however, were found in the paraffin cut sections although chloroform was used in the preliminary preparation instead of Xylol and the work was repeated several times with scrupulous care.

IV. Staining Methods Employed.

The following stains were used:-

(1) General Stains:-

(a) Haemalum and Eosin.

(b) Harris's Haematoxylin and Eosin.

(c) Van Gieson's stain.

(2) Stains for the Myelin-sheaths.

(a) For early degeneration. (1. Donaggio's Methods.
(2. Marchi's method.

(b) For late degeneration. (Weigert-Pal method.

(3) Stains for Nerve Cells and their processes.

(a) Toluidin Blue.)
(b) Thionin Blue.) Nissl gramules.
(c) Methylene Blue.)

(d) Williamson's modification of Bielschowsky's method.

(4) Stain for Neuroglia.

Weigert's modification of van Gieson with Iron Haematoxylin.

V. Summary of the Histological Changes found in the nervous System.

The histological changes may be best appreciated by a perusal of the numerous photomicrographs with their accompanying descriptive notes. Only a few remarks, therefore, will be required here. The three brains and spinal cords were examined. The changes found in each were very similar and served to substantiate each other. Any description applied to Case I applies equally well to Cases II and III. Portions of brains from children dying from other diseases were examined from time to time in order to control one's pathological technique. This had also a salutary effect in crushing any unconscious preconceived ideas, shattering ill-

founded interpretations of microscopical appearances, and led to the exposure of numerous artefacts. The control case which figures in some of the photographs was obtained from a female child of exactly the same age as Case II. She had suffered from abdominal tuberculosis and had no symptoms pointing to cerebral disease. To make the comparison as trustworthy as possible the brain from the control case was also fixed in Müller's fluid, and during the whole research received exactly the same treatment as the cases under investigation.

It may be remarked at the outset that the pathological histological results obtained are characterised by two features.

(1) A varying degree of degeneration of the pyramidal cells in the cortex cerebri, Purkinje cells in the cerebellum, and large angular cells in the spinal cord.

(2) A degeneration of the motor tracts in the brain and spinal cord.

Examination of the membranes of the brain and spinal cord and of the blood vessels revealed nothing which could be deemed abnormal.

No appearances suggestive of inflammatory reaction were found.

In a large series of sections, stained by the Donaggio and Marchi methods for early degeneration

of the medullary sheaths nothing abnormal could be found. This statement applies to Brain, Spinal Cord, and Nerves.

Cerebrum.

Generally speaking, attention was chiefly focussed upon sections from the following regions:-

1. Motor area (ascending frontal convolution)
2. Sensory area (ascending parietal convolution)
3. Mid frontal convolution.
4. Visual areas.
   - Angular gyrus.
   - Cuneate lobule.
   - Occipital poles.
5. Auditory area (superior temporal convolution)

In all these areas, cells in various stages of degeneration could be found. In some the usual concave margins of the pyramidal cells were convex. Other cells were globular or irregularly quadrate in shape. The body of the cell stained rather faintly with eosin. Sometimes the stain did not appear to "bite" at all and it was with difficulty that the shape of the cell could be distinguished. A granular mass was frequently the sole indication of the position of a cell. No nuclei were observed in some cells while in others the nucleus was eccentrically placed. Basic dyes should not stain normal nucleoplasm but this abnormal staining could be detected in some degenerated nuclei. Sometimes no nucleolus could be distinguished. The results obtained with stains for

the detection of Nissl's granules revealed none or at least very few. With Bielschowsky's silver impregnation method, no good specimens with neurofibrils coursing through the cells could be obtained.

As a control statement to the above histological findings, it must be mentioned that the results are not trustworthy. Several very just criticisms can be made. Practically every text book on microscopical methods mentions the fact that potassium bichromate, as in Müller's fluid, should not be used for the study of nerve cells. Mallory and Wright's textbook states (p. 121) that as it penetrates and hardens so slowly it does not preserve the ganglion cells and neuroglia fibres properly, while Bolles Lee (p.378) states that "according to the unanimous judgment of all investigators, the bichromate of potash should not be employed for the cytological study of nerve-cells." Hence my results regarding cell changes (in contra distinction to axis-cylinder and myelin sheath changes) are open to very serious objection. In carrying out the Bielschowsky staining too, great trouble was caused by the interaction of the silver bath and the bichromate, whereby numerous precipitates were produced in the tissues. The gramular appearance produced will be observed in some of the photo-micrographs. Another potent objection is the fact that 27-32 hours elapsed before the autopsies were performed and so many of the cell changes, such as the disappearance of Nissl's granules, may be due to post-mortem changes. With the control case which was also fixed in Müller's Fluid the

cytological changes were intense.

Subcortical white matter.

In the Rolandic area the subcortical white matter was not stained so intensely with the Weigert Pal method as the white matter in the other convolutions, thus proving the presence of some degeneration. Some of the radial fibres were varicose and attenuated. There was a slight scarcity of tangential fibres. The white matter at the occipital poles stained well with Weigert Pal as did also the white line of Gennari in the cortex in the neighbourhood of the calcarine fissure.

Basal Gaglia.

In the optic thalamus, caudate nucleus and lenticular nucleus, cell changes were seen similar to those already described as occurring in the cortex cerebri. In horizontal sections of the internal capsule, there was a definite paleness in colour even to the naked eye, when Weigert Pal sections of this part were compared with the colour tint of sections of the white matter of the centrum ovale. The fibres stained a dirty brown colour instead of a deep bluish black. Some especially in the posterior limb of the internal capsule were almost colourless and appeared to be thin and varicose. There was not such a definite loss of colour here as in the region of the pyramidal tracts in the spinal cord.

Mid-Brain.

Sections at the level of the superior and inferior

corpora quadrigemina were made. The crustal or ventral part appeared to be shrunken and did not seem to be large enough relatively to its tegmental or dorsal part. Degeneration was demonstrated by the Weigert Pal method in the middle third or pyramidal part of the crusta, but this was also noted in the two lateral thirds, i.e. cortico pontine, and geniculate portions. The fibres at the decussation of the superior cerebellar peduncles stained well as did also the longitudinal tracts forming the posterior longitudinal bundle, the mesial and lateral fillets. The fasicles of the third nerve stained well and were very prominent as they coursed through the red nuclei. The cells in the grey matter of corpora quadrigemina and other parts of the mid brain showed evidence of degenerative processes in their protoplasm and nuclei.

Cerebellum.

Marked atrophy of the folia was apparent even with the naked eye. Specimens from control cases when mixed with those from the patients under discussion could easily be separated without the aid of a lens simply by taking cognisance of the size of the folia. They were very thin as compared with the normals and moreover stained less deeply with ordinary dyes. The outstanding microscopic feature was the small number of Purkinjé cells - in fact it was a comparatively easy matter finding some laminae with no Purkinjé cells at all; The same could not be said of the controls - in them the

Purkinjé cells were numerous even in those portions of cerebellum suffering most severely from post mortem changes. (One cerebellum - the one figured in the photographs - was not removed till 30 hours after death and was also allowed to lie for two hours simply wrapped up in paper. It was also fixed in Müller's Fluid to put the comparison of results on an equal footing.) Whether there was a real deficiency in the numbers of the Purkinjé cells or not, it is difficult to say. I am inclined to think there was no diminution in the number of these cells. At first sight only a few Purkinjé cells in a folium would attract the eye but on moving the slide and carefully travelling along the junction line between the granular and molecular layers the "remains" of many other Purkinjé cells could be found. Their last resting place, so to speak, was marked by a mass of stainable substance consisting of fine granules. In some places a pale-staining skeleton of a cell was observed.

In a normal cerebellum one finds the Purkinjé cells situated at the junction line between the granular and molecular layers. In the specimens from the cases under discussion this position relative to the other structures seemed to be frequently at fault. Many Purkinjé cells seemed to be situated in a position nearer to the white matter of the cerebellum, i.e. within the granular layer. It might be thought that the gramular layer had increased in thickness and travelled

beyond the position of the Purkinje cells into the region of the molecular layer. This was not the case - in fact the granular layer was narrower and contained fewer cells than normal. The increased zone, i.e. the cells lying round the Purkinje cells and encroaching into the molecular layer, was not composed of granule cells but of cells half as large again as the typical granule cells. They look lighter in colour than the granule cells as they have a relatively small nucleus and a granular protoplasm. To use a very rough simile - the granule cells looked like small lymphocytes, - the other cells like leucocytes. I am not competent to judge but these may be large neuroglia cells, playing the role of phagocytes, and taking up the fat from the decayed Purkinje cells. Scharlach-stained specimens might throw light upon this subject. Mott, in his article on Amaurotic Family Idiocy in the Proc. Roy. Soc. Med., March 1911, p.193, speaks of Alzheimers Körnchenzellen cells and gives some valuable information upon the subject of fat changes. If Batten's figures of the cerebellum in his juvenile cases (fig. 8 and 9 in the "Quarterly Journal of Medicine" July 1914) be perused, a similar appearance to that which I have just described will be noted. In looking for skeleton forms of Purkinje cells the possible abnormal position of some should be remembered. With Bielschowsky's stain, swelling of the dendrites may be observed and about two cells' breadths distance from the cell there is often a very marked swelling of the dendritic processes. Such appearances are said to be a special feature in Tay Sachs'

disease. Regarding the changes in the Purkinje cells themselves, little more may be said. All degrees of degeneration were observed and this is well illustrated in the accompanying photographs.

The dentate nuclei cells were slightly degenerated. The surrounding white matter appeared to be normal. There was occasionally a slight patchy degeneration, however, as can be made out in one of the photographs. The superior, middle and inferior peduncles stained normally.

Pons and Medulla.

Sections were cut through the upper, middle and lower parts of the Pons. In the medulla they were chiefly cut at the following levels

(a) motor decussation.

(b) just above motor decussation.

(c) through level of middle of olivary body.

(d) near junction with pons.

The changes may be briefly summarized as a variable degree of degeneration of the nerve cells and a degeneration of the motor tracts.

Spinal Cord.

Sections through the sacral, lumbar, mid-dorsal and cervical regions were made. In all there was marked degeneration of the motor tracts with the Weigert Pal method. As the direct pyramidal tract normally only reaches down to about the middle of the dorsal region

the degeneration in it is only seen in the photographs above this level. The degeneration of the crossed pyramidal tracts may be seen as far as the lower sacral region. It appears to be nearer the surface there, however, as the direct cerebellar tract, which usually separates it from the edge of the cord is not normally present in this region. It might be objected that perhaps those tracts were never myelinated. The following will be interesting data, however, as tending to prove that there was a real degeneration of already existing myelin.

(1) The age of the children. The direct and crossed pyramidal tracts medullate soon after birth.

(2) There are normal looking fibres among the sclerosed ones - this would suggest that some at least were myelinated.

(3) The tracts look normal in size &c. Would this have been the case if there had been a developmental error?

(4) There is a slight indrawing of the edge of the section in some places opposite the degenerated tracts. This indrawing suggests a process of sclerosis.

(5) Absolute proof of course would have been secured if I had obtained degeneration with the Marchi method as it depends upon the presence of already existing myelin.

The nerve cells in the spinal cord showed varying degrees of degeneration.

Generally speaking there was proliferation of neuroglia in the sclerosed areas.

Nerves.

Nothing noteworthy regarding examination of 3rd, 4th, 5th, 6th, 7th, 8th and 12th cranial nerves, also regarding a small portion of ulnar nerve.

Viscera etc.

Nothing noteworthy regarding microscopic examination of thyroid, thymus, liver spleen, pancreas, small and large gut, and uterus obtained from Case II.

Remarks.

In contra-distinction to the symptomatology, all investigators (with perhaps the exception of Spielmeyer) are agreed upon the very close similarity in regard to the pathology between the infantile and juvenile forms of Tay Sachs' disease.

Regarding this statement by Sachs* - "While there is a superficial resemblance between the cell changes in these two varieties of amaurotic family idiocy, the differences are still more striking. In the juvenile form the disease process is not as universal as in the infantile form.....and we fail to find the typical balloon-like enlargement of the cell bodies and

* Jour. Exper. Med. 1910, XII, 685.

the swelling of the dendrites so characteristic of the cells of the Tay Sachs' type." ----- Wolfsohn points out that his juvenile case does show swelling of the dendrites &c. I have also noticed it in some of Bielschowsky's photographs. The histological findings in both types of the disease have been carefully described by various authors and there is no need to give a summary here.

Conclusion.

Dr. Findlay's cases, which form the subject of this paper, bear a very close resemblance pathologically to both the infantile and juvenile types of Tay Sachs' disease.

Fig. 48.

×8

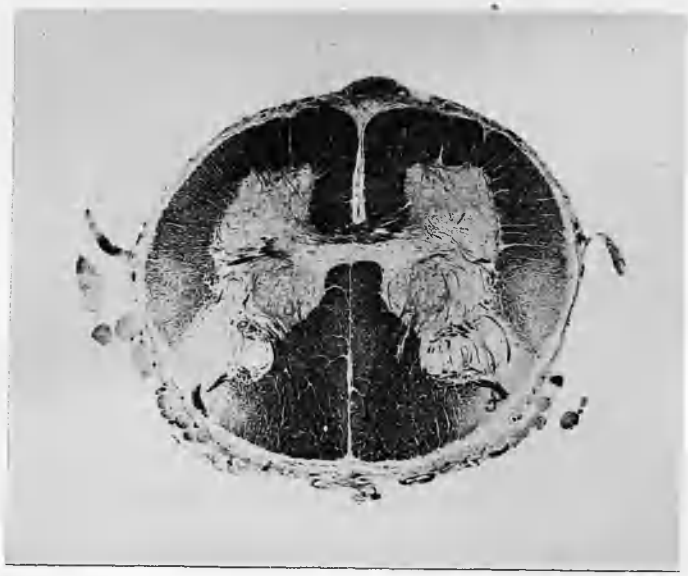
Fig. 49.

×7.

Fig. 48. (Case III.) Trans. section through the sacral region of the spinal cord. A naked-eye sclerosis of the crossed pyramidal-tracts is seen. [Weigert-Pal] Celloidin Sect.

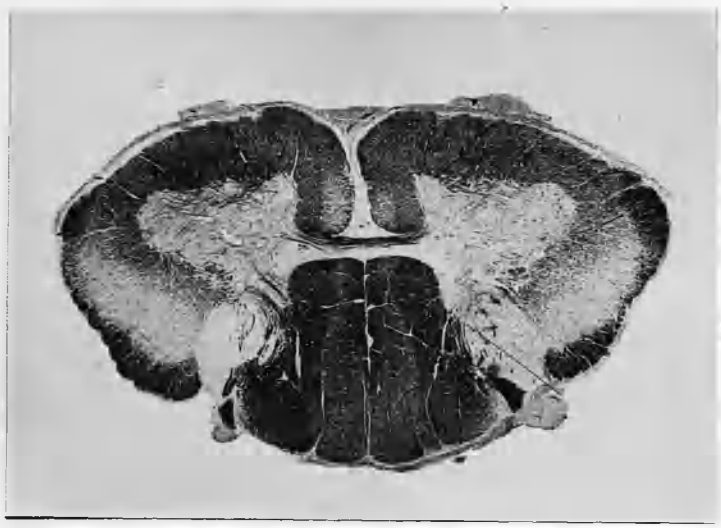
Fig. 49. (Case III.) Transverse section through the lumbar region of the spinal cord showing pale-staining in region of the crossed pyramidal tract. The direct-cerebellar tract does not normally reach as far down as the lower part of the cord & so no conclusions may be made regarding its condition as yet. Moreover since it is more or less absent in this region the crossed pyramidal tract may be considered as being represented by the fibres reaching practically to the outer edge of the spinal cord. There is also no direct pyramidal tract normally in the spinal cord until one gets above the mid-dorsal region. [Stained by Weigert-Pal method] Celloidin section.

Fig. 50.



× 8

Fig. 51.



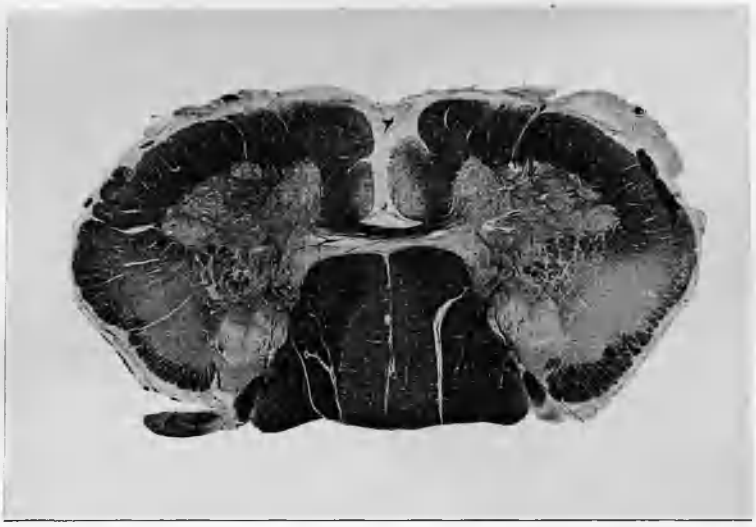
← puckering

× 7

Fig. 50. (Case "A.H") ie. Case III.
Transverse section through the dorsal region of the spinal cord showing the marked difference between the pale-staining crossed pyramidal tract + the darkly staining posterior columns ones
(Weig. Pal) The anterior + posterior roots have darkly staining fibres altho' this is not seen well in this photograph. This as Mott + others have pointed out is important as showing that altho the ant. + post. horn cells are degenerated the axons are still able to functionate.

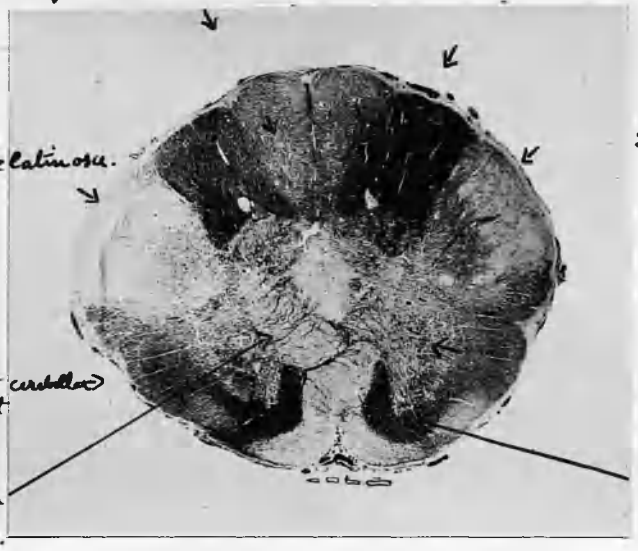
Fig. 51. (Case III) Trans. sect. through cervical region of cord. The sclerosis of the crossed pyramidal tract looks very
(Weig.-Pal) complete indeed but microscopically there was variation in the amount of degeneration in the fibres. Note the indrawing or slight concavity at the edge of the section opposite to the portion of the direct cerebellar tract which intervenes between the crossed pyramidal + the surface. This suggests a sclerosing action. Direct pyram.l is pale.

Fig 52.



× 7

Fig 53.



× 5

Fig. 52. (Case III) Trans. section through the cervical region near its junction with the medulla. The degeneration of crossed + direct pyramidal tracts is marked. The direct cerebellar tract stains darkly. (Weigert-Pal.)

Fig. 53. Trans. Sect through the lower end of medulla showing the decussation of the pyramids. The fibres are much degenerated. (Weigert-Pal)

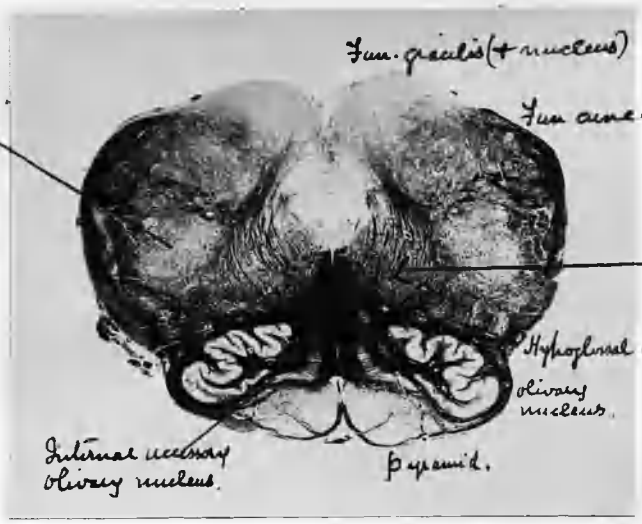


Fig 54.

× 3·5

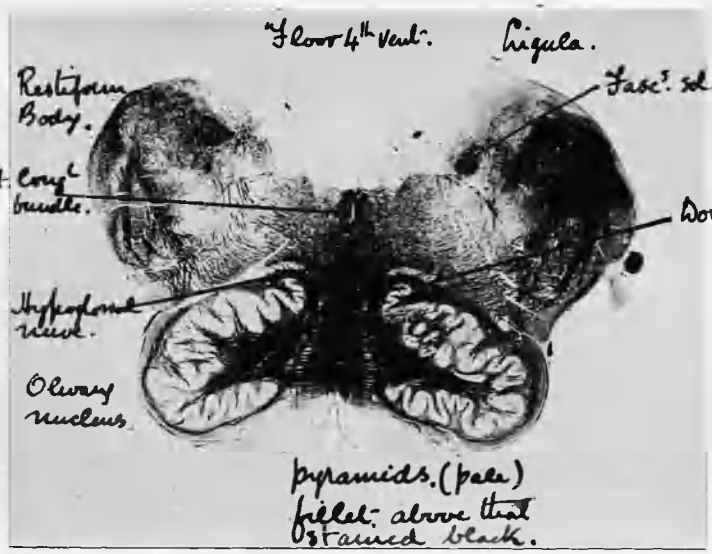


Fig. 55.

× 3·5

Fig. 54. (Case I) Transverse section of medulla a short distance above the decussation i.e. cuts through the lower part of the olivary body (Weig. Pal)

Fig. 55. (Case I) Trans. sect. thro' medulla about middle of olivary body. The degeneration of the pyramids is very marked.

Fig. 56.

x 3·5

Fig. 56

Transverse section of junction of ~~junction~~ of pons & medulla showing marked degeneration of the pyramidal tracts.

Celloidin Sect. (Weig. Pal.)

Fig 57.

× 3·5

Fig 58.

3·5

Fig 57. Transverse section through upper part of Pons from Case II showing marked degeneration of motor tracts.
Celloidin Sect. (Stain Weig. Pal)

Fig 58. Transverse section through upper part of Pons (near its junction with mid brain) showing degeneration of motor tracts.
Celloidin section. (Weigert Pal)

Fig. 59.

× 4.

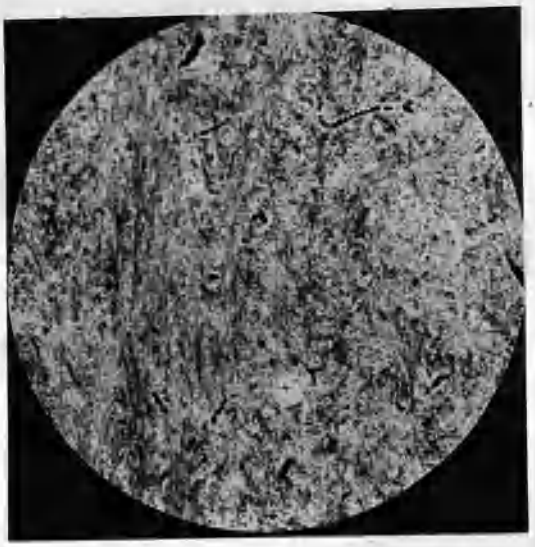
Fig 60

× 3·5

Fig 59. Transverse section through midbrain at level of inferior corpora quadrigemina showing the lack of staining in the motor tracts. (Weigert-Pal)

Fig 60. Trans. section through midbrain from case II at level of superior corpora quadrigemina. A portion of this part of the brain was destroyed at the post mortem so the section is incomplete.

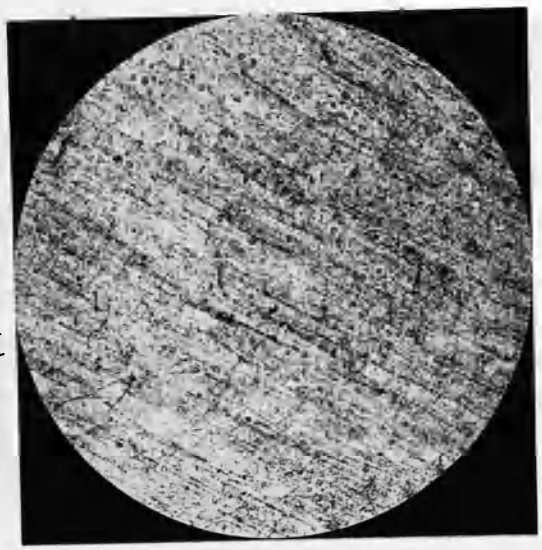
Fig. 61.
(Int. Capsule)



x 200

Fig. 62.

Subcortical white matter motor area.



x 200

Fig 62. Subcortical white matter from the Rolandic area of the brain stained by Weigert-Pal. The fibres were unevenly stained

Fig. 61. Internal capsule - motor area - showed some patchy pale areas. (Weig. Pal)

Pathological Description of the Optic Nerves, chiasma, tracts, and radiation.

Macroscopical examination:-

A comparison of the optic nerves and tracts with "control" cases showed them to be thinner and harder than the normal controls.

Microscopical examination:-

As will be seen from the accompanying micro-photographs the Weigert-Pal stain revealed degeneration of the optic nerves and tracts. No result was obtained with Marchi or Donnagio staining methods.

In toxic amblyopia, although there are no opthalmoscopic appearances at the macula, it is well-known that the papillo-macular fibres of the optic nerve are specially affected. In the present atypical cases of Tay-Sachs disease with no macular opthalmoscopic appearances I considered it a possibility that here there might also be a special pre-dilection for the papillo-macular bundle but I can find no references to this in the literature on the subject.

The papillo-macular bundle changes its position relative to the other fibres, as it travels backwards towards the chiasma. Hence sections at various levels must be taken in order to trace its course. This is very well shown in the accompanying diagrams from Dr. Maitland Ramsay's book. Just behind the eyeball the bundle occupies a rough triangular area

on the outer side of the nerve. About half way between the globe and the chiasma the bundle is centrally-inclined and still further back it is quite central. I cut transverse sections as follows:-

(1) 1/8"-1/4" behind the eyeball.

(2) Halfway between the eyeball and the chiasma.

(3) Just in front of the chiasma.

(4) Just behind the chiasma (i.e. through the tracts).

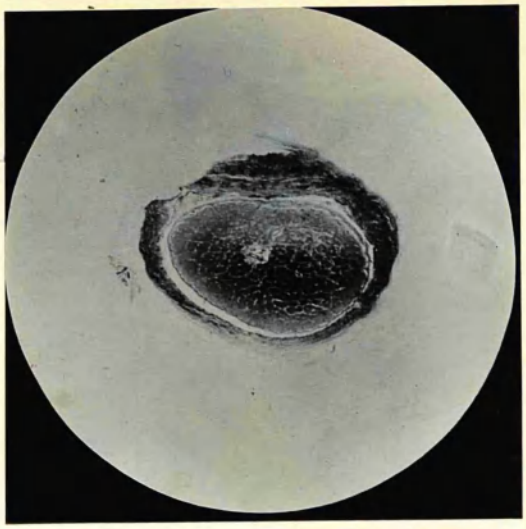
Also antero-posterior horizontal sections through the chiasma. Although the papillo-macular bundle is somewhat degenerated, it does not seem to be specially involved. It will be observed that <u>other</u> parts of the nerve are also affected and that the degeneration is "patchy". Attenuation and varicosity of fibres was present in some parts of the optic chiasma and to a less extent in the optic radiations at the sides of the posterior horns of the lateral ventricles. The dural and pial sheaths of the optic nerve were normal. No inflammatory exudation was observed. No abnormality could be detected in the central artery and vein. Atrophy of the optic nerves and tracts is present in both the infantile and juvenile form of Tay-Sachs disease.

<u>Conclusions</u>.

I. The present cases resemble the infantile and juvenile forms of Tay-Sachs disease in possessing degeneration of the optic nerves and tracts.

II. There is apparently no special predilection of the degenerative process for the papillo-macular bundle.

Fig. 63.

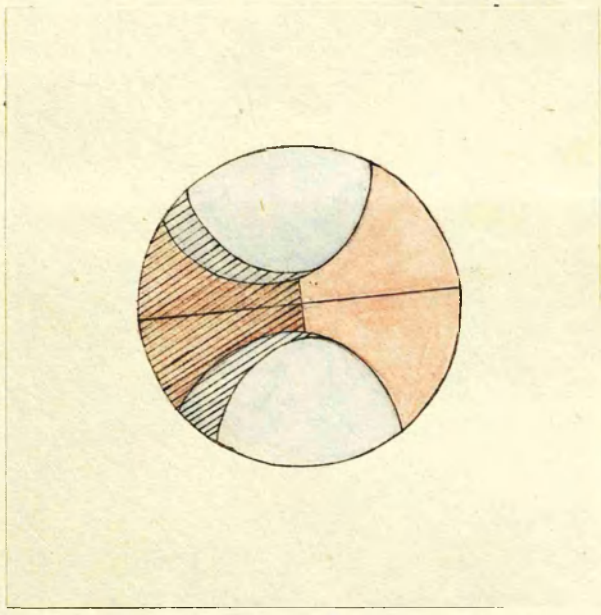


left. right.

× 9.

left.

Fig. 64.

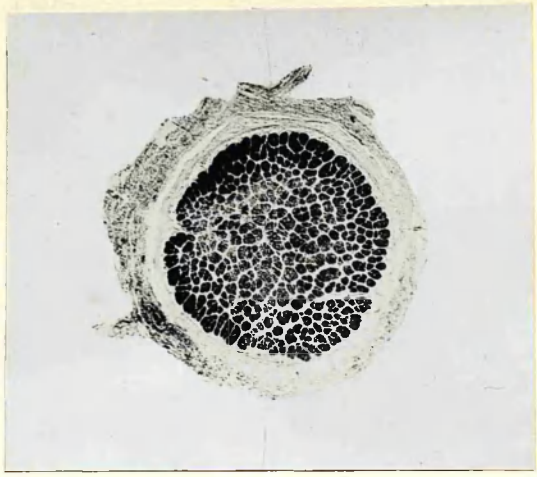


right.

Fig 63. Transverse section of left optic nerve stained by Weigert-Pal method. There are some patchy degenerated areas. The section was taken just behind the eyeball.

Fig. 64. Diagrammatic transverse section, the region of the papillo-macular bundle is shaded. (After Maitland Ramsay - vide description in text of thesis.)

Fig 65.



X 12.

Fig. 66

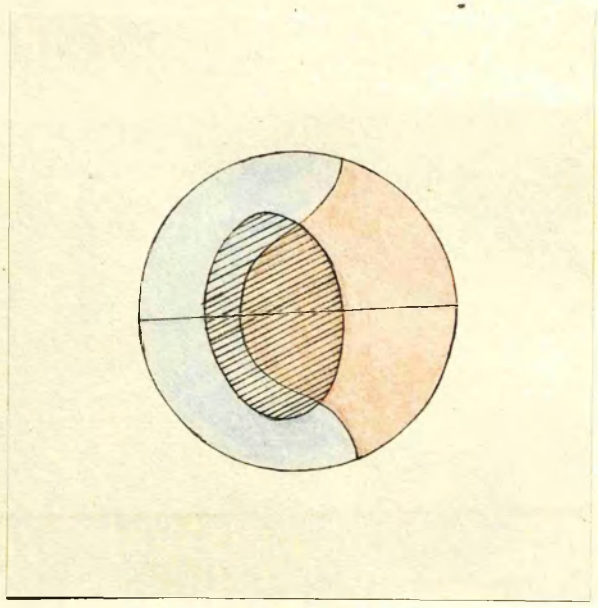


Fig. 65. Trans. Sect. of left optic nerve midway between the eyeball + Chiasma. Stained by Weigert-Pal.

Fig. 66. Diagrammatic representation of the position of the papillo-macular bundle (shaded.) After Maitland Ramsay.

Fig. 67.

left. right.

x12

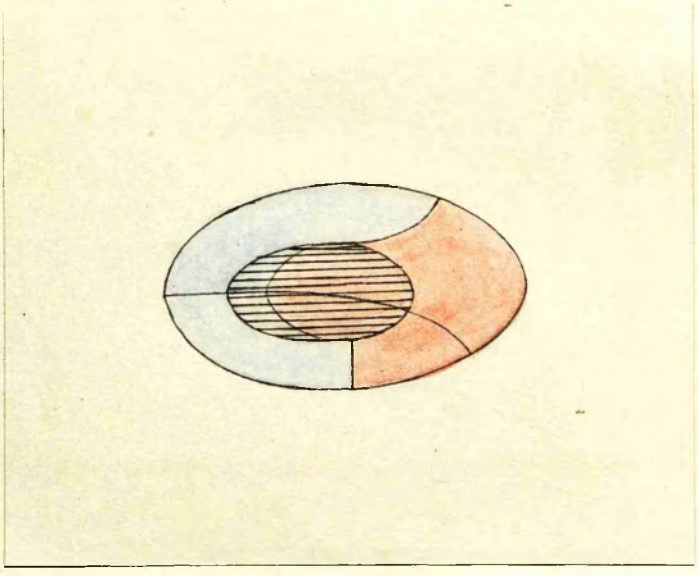


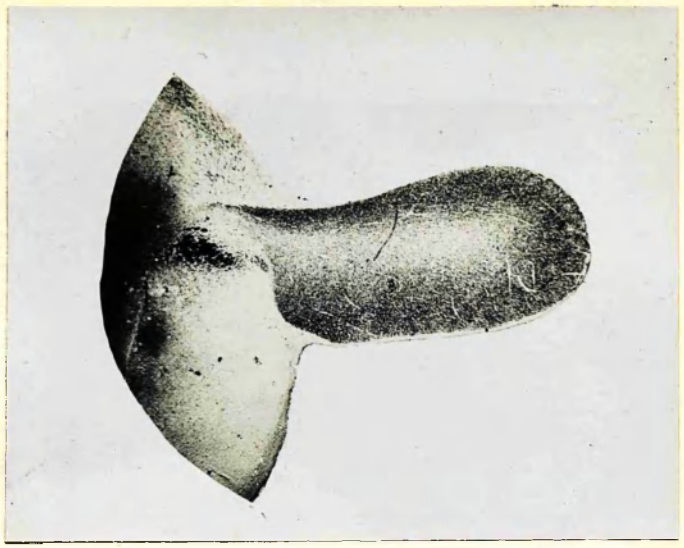
Fig 68.

left. right.

Fig 67. Transverse section of left optic nerve just in front of the optic chiasma showing the position of the patchy degeneration. (Weigert--Pal Stain)

Fig. 68. Diagram of position of papillo-macular bundle to compare with the above. Shaded area = papillo-macular bundle. (after Maitland Ramsay)

Fig 69.



X12

Fig 70.

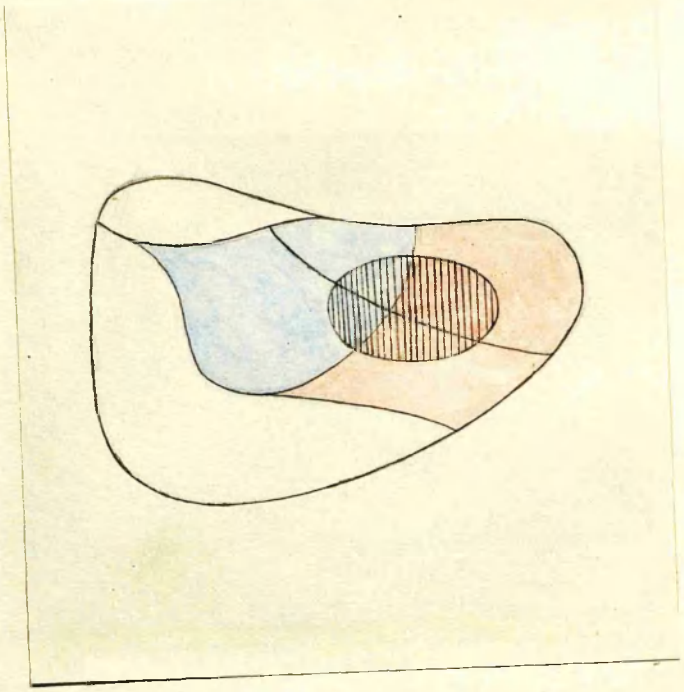


Fig. 69. Transverse section of left optic tract just behind the chiasma. Stained by Weigert Pal method.

Fig 70. Diagram to compare with above. The shaded area is the position of the papillo-macular bundle. (after Maitland Ramsay.)

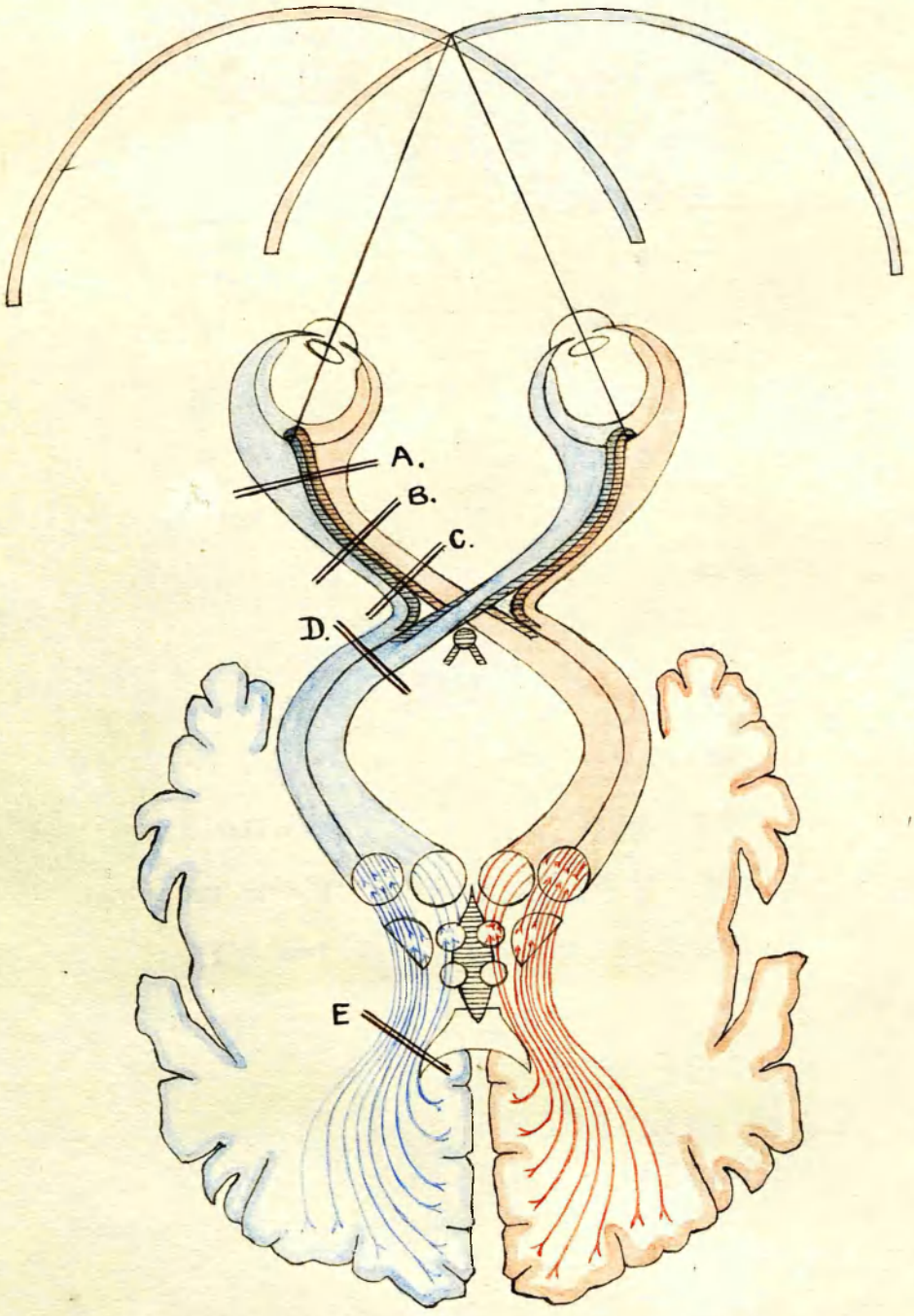


Fig. 41.

"Those parts of the visual apparatus that are connected with the right side of the brain, as well as the portions of the visual fields from which they receive their visual impressions (viz. the left-sided portions of the visual fields), are represented in pink: the parts connected with the left side of the brain (together with the right-sided portions of the visual fields) are represented in blue. The papillo-macular bundle of the optic nerve is shaded." (A. Maitland Ramsay, "Clinical Ophthalmology, p.378).

A. - Section of optic nerve close to eyeball.

B. - Section of optic nerve midway between eyeball and optic chiasma.

C. - Section of optic nerve immediately in front of optic chiasma.

D. - Section of optic tract, immediately behind optic chiasma.

E. - Section through optic radiation at side of post. horn of lateral ventricle.

Pathological Description of the Retinae.

The following results refer to Cases II and III as the eyes in Case I were unfortunately not preserved.

At the autopsies, the posterior half of each eye was removed and placed in formalin, while one small portion, after preliminary formalin fixation was treated with Müller's fluid plus 2% Chrome-alum in preparation for Weigert staining.

Macroscopically nothing abnormal could be detected. In the infantile form of Tay-Sachs' disease, a discoloured area may be visible at the macular region, but careful search revealed nothing in the atypical cases described in this thesis.

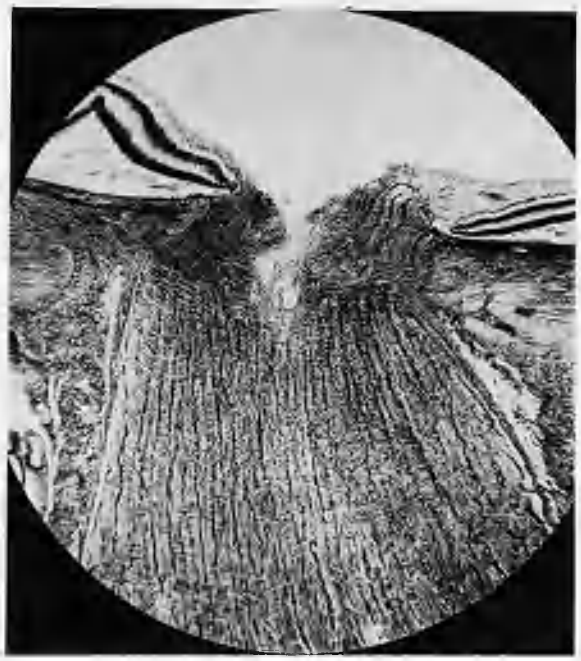
Microscopically Examination was in every instance conducted on celloidin sections, which, for retinal work, are infinitely superior to paraffin ones. The following stains were used: Haemalum and Eosin: Haemalum and van Gieson: Harris' Haematoxylin and Eosin: Thionin Blue: and Weigert-Pal.

Formalin is described by Coats as being the worst of all retinal fixatives while Shumway and Buchannan show that the retina is almost inevitably detached from the choroid and thrown into folds when Müller's solution is used. (This occurred in one of the Tay Sach's cases which they examined). Be that as it may, the retinas in the present cases were certainly separated and thrown into folds in many places while still in the fixatives, and I was unable

to find the maculae for section cutting. In some places, the separation occurred at the pigment layer, in others at that of the rods and cones. At some parts the layer of optic nerve fibres was thinned, and stained badly with ordinary dyes. With the Weigert-Pal method no conclusions, of course, could be drawn as to the state of this layer as the fibres normally possess no medullary sheaths after passing through the lamina cribrosa sclerae to reach the retina. Some ganglion cells had eccentric nuclei, others none at all, while the protoplasm of some stained so faintly that their outlines were detected only with difficulty. In a few cells, vacuoles were seen. No Nissl's granules were observed.

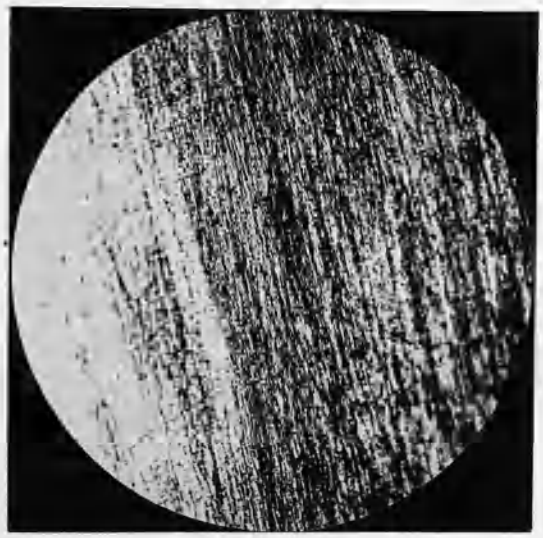
Assuming that in a normal retina, (travelling in a horizontal meridian from the optic disc, and excluding the macular region), there is roughly a depth of 3-4 ganglion cells, at a distance of 3 discs' diameter from the optic disc, and 2-3 cells at 4 discs' diameter, and thereafter towards the periphery only a single layer of scattered cells, I found a diminution of ganglion cells in many places. Whether this was due to post-mortem change, an actual deficiency in numbers, or a real degeneration, I am unable to state. The inner and outer nuclear layers were apparently normal. The thickness of the inner molecular layer varied considerably in different situations. That was also the case in the outer molecular layer (often called the inter-nuclear layer) especially in its outer portion, which had in many

Fig 72.



X 25

Fig 73.

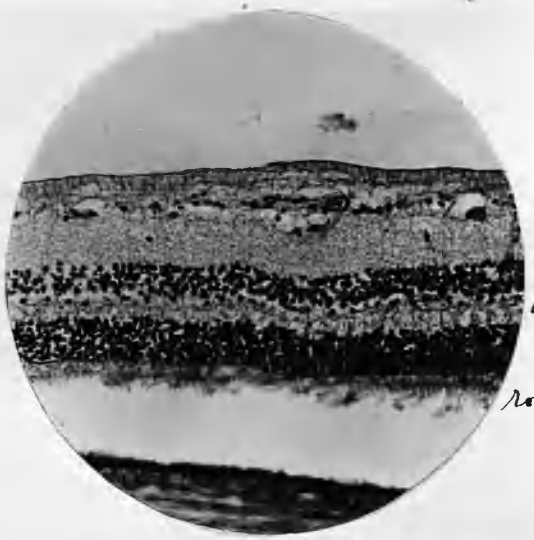


X 200

Fig 72. Transverse horizontal section through optic nerve at its entrance to the retina. Stained Harris' Haematoxylin + Eosin.

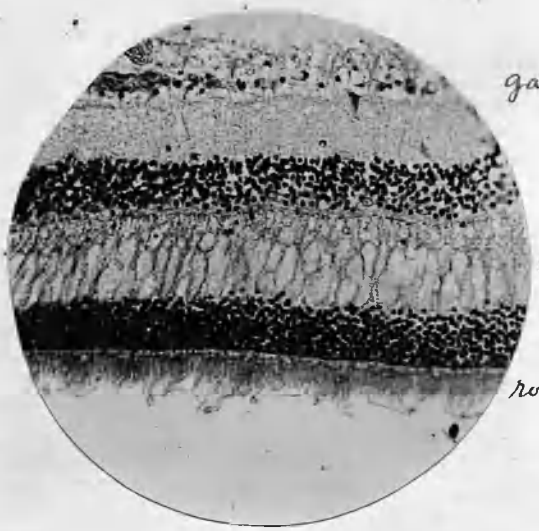
Fig 73. Horizontal section through left optic radiation showing some patchy staining. (Weigert-Pal Stain)

Fig. 74.



× 200

Fig 75.



× 200

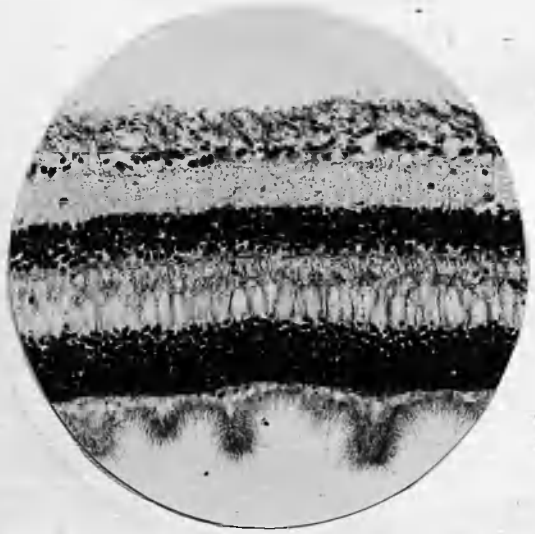
Fig. 74 + 75 are taken from the same piece of retina. To illustrate the varied appearance produced by the degree of obliquity with which the retina is cut. Note the difference of the thickness of the molecular layer at (a)

Fig 76.

1. nerve fibre layer
2. ganglion cells.
3. Inner molecular.
4. Inner nuclear.
5. Outer molecular.
6. Outer nuclear.
7. Rods + cones.
8. Pigment.

X 200

Fig. 77.



1. nerve-fibre layer.
2. ganglion cells.
3. Inner molecular.
4. Inner nuclear.
5. Outer molecular.
6. Outer nuclear.
7. Rods + cones.

X 200

Fig. 76 + my 77. to illustrate the appearances of the different retinal layers described in the text. Both sections were taken from the same retina. Stained by Harris's Haematoxylin + Eosin.

Fig. 78.

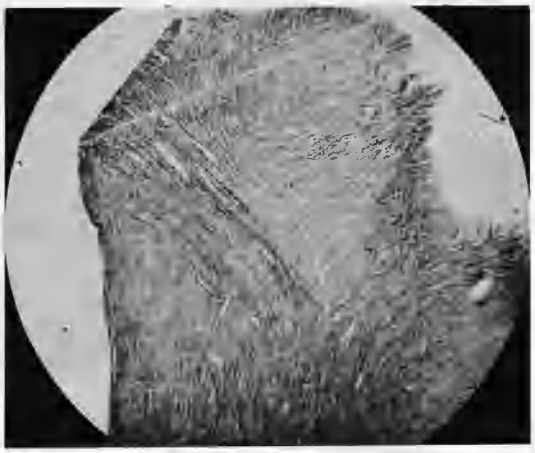
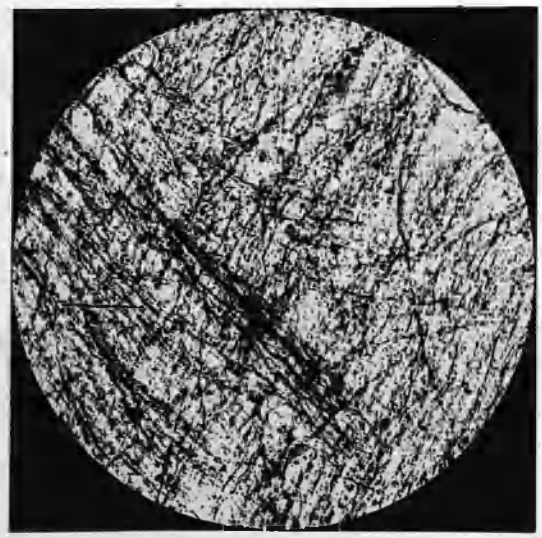


Fig. 79.



x 200

Fig. 78. Antero-posterior horizontal section of optic chiasma. The fibres did not stain well.
(Weigert Pal)

Fig. 79. High power view of above showing some decussating fibres with varicosities.
(Weigert-Pal)

places, a web-like or vacuolated appearance. Normally as may be seen from text-book diagrams, the outer molecular layer is narrower than the inner. In some places in the present specimens, the opposite appearances were noted. I ascribed this at first to an oedema, but in view of the fact that this appearance could be altered by cutting the section very slightly obliquely, such an opinion could not be entertained with any degree of certainty. As already stated, the retina was separated from the choroid in many places, and naturally the folds or corrugations would be cut obliquely in some parts. The layer of rods and cones showed marked degeneration, and frequently total disintegration - the outer segments being more affected than the inner ones - a condition observed in many normal retinas and due no doubt to post-mortem change and the method of fixation (vide Bolles Lee). Any migration of retinal pigment which was observed into the outer layers of the retina was evidently due to a mechanical peppering of that part, caused by the artificial separation of the retina. In every instance, it coincided with a ruptured portion of the retina. No changes were detected in the retinal or choroidal blood vessels. There was no inflammatory reaction and the choroidal and sclerotic coats were normal.

Discussion.

To give a truthful interpretation of results obtained from the histological examination of any retina, not

obtained immediately after death, or post-operatively, is a matter of great difficulty. Coats says that any histological study is valueless unless the following three conditions are satisfied:-

"(1) The material must be absolutely fresh - according to Birch-Hirschfeld post-mortem changes begin within two hours of death.

(2) Fixation must be perfect, Zenker's Solution being by far the best for this purpose, especially in the intact globe.

(3) The method of cutting must be suitable, paraffin being greatly inferior to celloidin, even with the greatest care, and the best fixed material."

He then proceeds to state that "Insistence on these pre-requisites eliminates nearly everything that has been written on the histology of the retina in amaurotic family idiocy .....not more than three or four cases have been recorded to which no exception can be taken."

As far as can be ascertained, the eyes in the present cases were not removed till 24-30 hours after death, and no preliminary injection had been made into the eyeballs immediately after death. They were fixed in formalin (the worst of all retinal fixatives, according to Coats). Embedding and cutting were carried out in celloidin. Although only one condition was thus satisfied, I deemed it advisable, in view of

the fact that Batten and Mayou had in one of their cases of Family Cerebral Degeneration (Juvenile Tay-Sachs) found in some places such marked changes as "complete disappearance of the inner nuclear layer, ganglion cells and the rods and cones", to continue the pathological examination. Nowhere did I find complete disappearance of any of these layers.

In order to discuss the relationship of the retinal histology between the Infantile and Juvenile forms of Tay-Sachs disease and the present cases, some data must be given.

A. Retinal Histology in Infantile Tay Sachs Disease.

Although oedema of the outer molecular layer (inter-nuclear layer) has been described in some cases of infantile Tay-Sachs disease (e.g. case described by Treacher Collins; Mohr's case referred to by Schumway and Buchannan; and the case illustrated in fig. 4 of Batten & Mayou's paper), it is now agreed that the changes are confined entirely to a degeneration of the ganglion cells, nerve fibre layer, optic nerves and tracts (Sachs). In the three or four cases referred to by Coats as satisfying his three pre-requisites, the authors specifically state that there was no oedema. In drawing conclusions, therefore, I think it will be prudent not to lay too much stress upon the presence or absence of oedema. While surveying the literature upon this subject, I have made the general observation that, in the earlier described cases, attention was chiefly focussed upon the oedema, and in all the more recent cases upon the ganglion cell changes.

The former school explained the white zone round the macular "cherry-red spot" as being due to oedema of the tissues, while the latter find a sufficient explanation of the fundal appearances in the degeneration and swelling of the ganglion cells (which normally are present in greater numbers at the EDGE of the macula than at any other part of the retina). Various arguments such as the presence or absence of veiling of finer vessels by oedema, the changing or unchanging appearance of the "cherry-red spot" supporting one or other theory, cannot be discussed here.

B. Retinal Histology in Juvenile Tay-Sachs Disease.

I have only been able to find three published accounts of the pathology of the retina in such cases.

It is doubtful whether the Stock-Spielmeyer cases should be included in the list as many points in the clinical histories suggest a syphilitic taint. Stock and Spielmeyer maintain that their cases are examples of an independent disease, but Gifford includes them in his list of juvenile cases. Oatman and Clark consider them to be quite irregular cases. They are definitely uncertain cases and I do not propose to discuss them further.

I. Ichikawa (Kyoto, Japan) in a child 7 years old, found a very marked degeneration, more or less complete, of all the retinal layers, but with Weigert the optic nerves stained normally as far as the chiasma. Speaking of the relationship of the diseases, he considers that "these different forms of primary retinal degeneration are probably produced by the same cause although their

clinical and anatomical characters in certain points appear to vary."

II. Wandless' Case (pathological report made by Brooks). Boy about 15 years old. The optic nerves were shrunken in size and microscopically they were so degenerated that practically no nerve fibres could be detected. Degeneration was so complete in the retina that the normal strata were indistinguishable. No ganglion cells found. Choroid normal. No mention made of method of fixation &c.

III. F. E. Batten & M. S. Mayou's case (Pathological report by Mayou).

This is an excellent account and the method of fixation, embedding etc., leaves nothing to be desired. It is interesting to note that the macular region was a situation of most marked histological change although clinically there was NO typical infantile Tay Sachs "cherry red spot" at that site. In some parts the retina was normal except for degeneration of the ganglion cells; in other parts the inner nuclear layer, ganglion cells and rods and cones had completely disappeared. The first stage in the degenerative process was a ganglion cell degeneration (exactly similar to that found in Infantile Tay Sachs). This was followed by slight oedema of the internuclear layer, and thereafter by a gradual disappearance of the inner nuclear layer, rods and cones. The final pathological sign was a migration of retinal pigment cells into the outer layers of the retina. Coupled with

these neural changes, there was a slight proliferation of the retinal supporting elements with their nuclei. Batten and Mayou state that their cases show a "close relationship" to amaurotic family idiocy (i.e. Infantile Tay Sachs).

I have arranged in tabular form the results obtained from a review of the aforementioned published reports. It will be noted from the accompanying table that ALL the juvenile cases show degeneration of the rods and cones and thus differ from the infantile group. Should this form the basis of a sharp distinction between the two types? Although the consensus of opinion is that the rods and cones are normal in the infantile group, there are accounts in which they are described as somewhat degenerate (e.g. Shumway and Buchannan's case and others).

The rods and cones show up the frailty of one's pathological technique in a most disconcerting way and in this respect my own results are not good. In fact, Bolles Lee, speaking of the necessity of proper and immediate fixation of the retina states that "after a few MINUTES a series of changes begins to take place by which the outer segment of both rods and cones become split into discs and finally disintegrate so as to be altogether unrecognisable, even if not totally destroyed." No strong argument, therefore, can be founded upon the condition of the rods and cones.

The degenerative condition of the molecular layers in the juvenile type might also form a subject of

contention. This, although not considered normal in the infantile type, has certainly been described in some of the cases (vide remarks under the infantile type). Moreover Mayou states* that in his own juvenile case the only histological appearance which could not be relied upon was "the slight oedema of the inter-nuclear layer" i.e. outer molecular layer, and hence in the table I have questioned it.

Very few retinae of the juvenile type have been examined and until we have more data, I think the groups should not be segregated.

* Vide Mayou's remarks in the discussion at the end of Coats' paper.

Case.	Ichikawa	Wandless	Batten & Mayou	Present Cases.	Infantile Tay-Sachs.
Age of patient	? 7 yrs.	15 yrs.	"H.B."= 6 yrs.	"M.H."=$3\frac{2}{12}$ yrs. "A.H."=$2\frac{5}{12}$ yrs.	Most die before 2 years old.
Condition of optic nerves.	x	x	No mention of nerves but states "but little change in optic tracts"	x	x
Nerve fibre layer.	x	x	x	x	x
Ganglion cells	x	x	x	x	x
Inner molecular	x	x	x	x(?)	0 (but x in a few)
Inner nuclear	x	x	x	0	0
Outer molecular (inter-nuclear)	x	x	x(?)	x(?)	0
Outer-nuclear	x	x	0	0	0
Rods & Cones	x	x	x	x	0 (but x in a few)
Pigment epithelium	x	x	x	0	0

x = Degeneration.
0 = No degeneration or almost normal.

Conclusions.

(1) The cases described in this paper being the youngest in the list, most closely resemble the Infantile Tay-Sachs group, with regard to the age incidence.

(2) Histologically they also resemble it, by possessing the typical pathological picture of degeneration of optic nerves, nerve fibre layer and ganglion cells (a triple syndrome).

(3) They present fewer additional variations to the accepted triple syndrome than the other cases. Of these additional irregularities, most certainly the degeneration of rods and cones may be discounted, owing to post mortem change and method of fixation.

(4) In the elder cases (i.e. Ichikawa and Wandless) the retinal destruction is most complete. This may be due to the patients having lived longer than in the Infantile Group, and so allowing the final stages of degeneration to take place.

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