INFANTILE CEREBRAL DEGENERATION

WITH

SYMMETRICAL CHANGES AT THE MACULA

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INTRODUCTION.

UNDER the above title we purpose to describe a rare and fatal disease of infancy, which commencing in the early months of infant life by muscular enfeeblement associated with distinctive ophthalmoscopic appearances, progresses to almost complete paralysis, and terminates in the death of the patient about the end of the second year.

So far as we know the disease has been chiefly recognised by ophthalmic surgeons, their recorded observations dealing mainly with the ocular symptoms.

Mr. Waren Tay first drew attention to the subject in 1881, and the references to his papers, and to those of others who have recorded instances of the affection, will be found in a bibliography at the end of this paper.

No autopsy could be obtained in any of the recorded cases, with the exception of a case reported by Dr. Knapp. A description of the changes found in the brain in this case is given by Dr. B. Sachs, of New York, in a paper entitled "Arrested Cerebral Development," a reference to which will also be found in the bibliography on the subject. The spinal cord and eyes were not examined in the case in question.

Three cases of the disease have been under the observation of one of us (Kingdon), and careful clinical investigation of the patients has been supplemented by post-mortem examinations together with a microscopical examination of the central and peripheral nervous systems and eyes in two of the cases which have terminated fatally. We propose, therefore, to give an account of these cases in the first instance, then to allude to one kindly placed at our disposal by Dr. F. J. Smith, and finally to draw attention to the leading characteristics of the disease, our description being based on a study of the recorded cases in conjunction with those that we are about to call attention to.

Cases observed by the Authors.

The patients were two brothers and a sister, born of strong and healthy parents, both of whom are German Jews. The parents are not related to each other, and no family history of any hereditary taint can be elicited.

The family consisted of seven children. The first, a boy born one year after marriage, was, according to the mother's statement, well developed at birth, but subsequently became weak in the back and limbs, and mentally apathetic; he wasted and died at two years of age in the Hull Infirmary, and was without doubt the subject of this complaint.

The second child, a girl, born ten months afterwards, is in good health at the present time.

The third child, a boy, born three and a half years afterwards (no miscarriages in the interval), was affected, and forms Case 1.

The fourth child, a boy, born April, 1892, is healthy.

The fifth child, a girl, born May 6th, 1893, was affected, and forms Case 2.

The sixth child, a boy, born November, 1894, is affected, and forms Case 3.

The seventh child, a boy, born November 21st, 1895, appeared healthy when examined on February 20th, 1896.[1]

CASE 1.—An account of this patient with the result of the autopsy was read by one of us (Kingdon) before the Ophthalmological Society in 1892, and was published in the 'Transactions' of the Ophthalmological Society of the United Kingdom, vol. xii, p. 126. The following is a brief abstract:

Jacob R—, aged 8 months, was admitted to the Children's Hospital, Nottingham, on account of a general increasing weakness of the back and limbs (Fig. 1).

The mother stated that the patient was born at full term, and until the third month was reached, he appeared to have similar strength to other children of the same age. He was fed by the breast until his admission, and had always been well nourished. There had been no convulsions or other previous illness. From the age of three months there had been increasing enfeeblement of the muscles of the back and limbs, the most obvious symptom being an inability to hold up the head.

On July 1st, 1891, the child, being nine months old, was 17½ lbs. in weight, 26½ inches in height, and had a well-shaped head 17½ inches in circumference. There were no external congenital defects; the body was well covered

[1] Since this paper was submitted to the Society, unmistakable evidence of the disease has been detected in the seventh child of the family. The sixth child (Case 3) died on May 6th, 1896; permission to examine the head was obtained, and a microscopical examination of the brain, cerebellum, pons, medulla, spinal cord, and eyes has since been made.

with fat; the muscles felt flabby, but any wasting was masked by the subcutaneous fat. The limbs moved feebly,

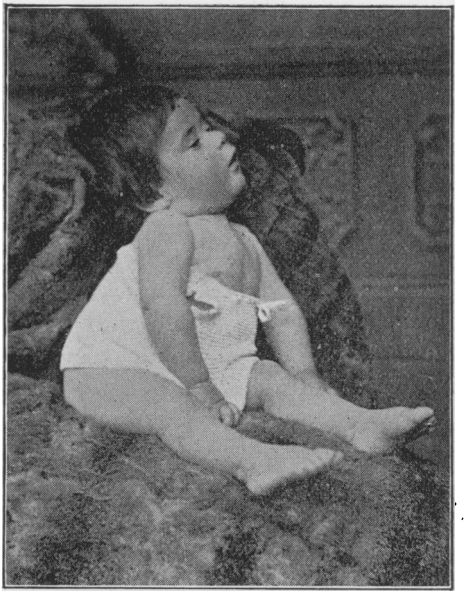

FIG. 1.—A photograph of the boy an abstract of whose case has been included in this paper as Case 1. The photograph was taken in October, 1891, and shows little beyond the cerebral expression of face, and the weakness of the neck muscles as evinced by the falling back of the head.

and though objects were grasped when placed in the hands, they were soon dropped. He was unable to turn on to either side when lying on his back. The knee-jerks were well marked. There was no rigidity of the limbs, but occasionally there were some short spasmodic contractions. The child was apathetic, and lay quietly in bed. Hearing was acute, with great sensitiveness to sudden noises. The eyes on external examination appeared normal, but no notice was taken of objects held in front of them; and on ophthalmoscopic examination symmetrical changes

at the macula were discovered. In this region there was a whitish-grey patch about twice the size of the optic disc, only slightly raised above the general surface of the retina, with a dark cherry-red spot in its centre. The thoracic and abdominal viscera were healthy, the appetite good, the bowels regular, the urine natural, and the temperature normal.

The child remained in much the same condition until October 16th, though more feeble and quite blind as a result of optic atrophy. He had increased 1 lb. in weight. Two days afterwards he became pale and shrunken, and gradually unconscious, with frequent moaning and low rhythmical movements of the eyes from side to side; the pupils were equal, moderately dilated, and inactive to light. There were no definite convulsions. The temperature remained normal, and there were no signs of disease in the chest. The condition resembled the attacks which occur during the later stages of general paralysis of the insane.

The patient became more lethargic, and died on October 20th, 1891.

Autopsy (eighteen hours after death).—The brain with the upper portion of the spinal cord and both eyes, were removed and placed in Müller's fluid. The thorax and abdomen were not examined. The posterior fontanelle was closed, the anterior fontanelle nearly so. There was no marked excess of cerebro-spinal fluid. The arachnoid and pia mater were neither thickened nor adherent, and there was no evidence of meningitis. The sulci over the whole surface of the brain were slightly wider than normal, but there was no irregularity in the arrangement of the primary fissures or convolutions. The distribution of the superficial blood-vessels was normal. The brain weighed 38 ounces.

Microscopical examination.—The microscopic examination of the brain and spinal cord was not so thorough as that which has been carried out by one of us (Russell) in the second case. Sections taken from the different cortical areas revealed very similar changes in all, viz. that the different layers of cells were not so readily distinguished

as is usual, the most marked alteration appearing in the large pyramidal cells, which had an oval or rounded outline. The protoplasm was vacuolated, and mostly collected into an irregular shrunken mass around the nucleus. The same changes were present in the small pyramidal cells. The basal ganglia were not examined.

Sections of the spinal cord at the level of the second cervical vertebra revealed well-marked descending degeneration.

Ocular changes.—The eyes were embedded in celloidin, and the changes found were similar in both. The retina was folded at the macular region ; the outer molecular layer of the retina in this area was spaced out and enlarged, but the other elements of the retina seemed healthy. The optic nerve was atrophied. The choroid was normal.

Treatment.—For the first two months after admission the child was given Pulv. Hydrarg. c. Cret. gr. ¼ twice daily. After this time no medicinal remedies were employed beyond such as were necessary to check any temporary alimentary disorder. Great attention, however, was devoted to the careful and regular feeding of the child, and to providing that its general surroundings should be as favorable as possible.

Case 2.—Bluma R—, sister of the above, born May 6th, 1893, was on August 5th, when three months old, brought to one of us (Kingdon) to have the eyes examined, as the mother thought her child was failing in the same way as the others who had died. On examination some weakness of the back and neck was observed, and the mother stated that the child "started" occasionally while asleep. The condition of the macula lutea and optic papilla was normal.

When five months old another examination was made. The muscular enfeeblement had advanced, and the child paid but little attention to objects placed in its hands or held before its eyes. Ophthalmoscopically there was a suspicious haze at each macula.

December 26th, 1893.—The child being now seven and a half months of age, was again seen, and admitted to the hospital, where it remained until its death. The general appearance, nutrition, and muscular weakness corresponded to that of the first case; but she was more fretful and less apathetic than her brother. Ophthalmoscopic examination revealed the typical changes in the fundus of each eye, similar to those met with in the boy. Hearing was acute, and the sense of taste preserved. The muscles at the back of the neck and intra-scapular region were obviously atrophied. The electrical reactions of the muscles were not tested. Cutaneous sensibility was apparently normal.

Her weight was 15 lbs. The appetite was good, the bowels regular, and there was no sickness. The heart, lungs, urine, and temperature were normal.

During the first fortnight after admission, the patient gained 1½ lbs. in weight, and on January 25th, 1894, was shown at a meeting of the Ophthalmological Society in London. After this temporary increase in weight no further improvement occurred; on May 2nd she still only weighed 16 lbs., and the subcutaneous fat, as well as the muscles generally, had wasted. Rigidity of the latter was now evident, the head was retracted, the left forearm pronated and partially flexed, with flexion of the fingers and thumb of the left hand, both the thighs were adducted, the legs extended, and the great toes extended at the metatarso-phalangeal and flexed at the inter-phalangeal joint.

During June the general aspect of the patient grew worse, the wasting and rigidity of the body increased, and the face wore a greater cerebral expression; the appetite remained good, and the temperature normal.

During July and August there were occasional attacks of vomiting and diarrhœa, and food was given with difficulty. The rigidity of the lower limbs was extreme, so that they could not be bent. The thighs were flexed on the abdomen, rotated inwards and adducted until the knees

crossed each other (Fig. 2). There was partial backward dislocation of the knee-joint from hyperextension of the

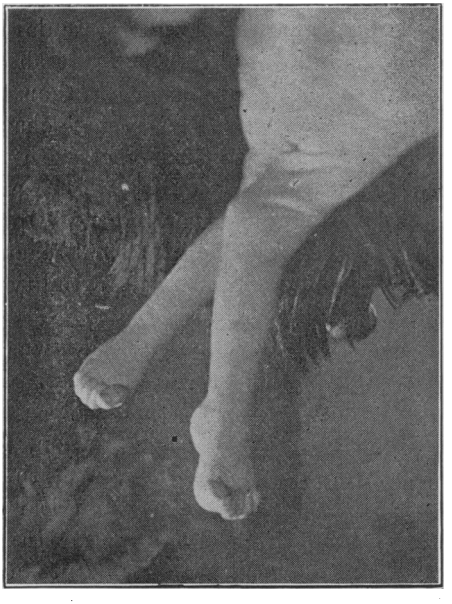

FIG. 2.—A photograph of the inferior extremities of the same case as that represented in Fig. 3, intended to illustrate the marked adductor spasm which was present at an advanced stage of the disease.

legs (Fig. 3). Both upper arms were rotated inwards, and the forearms pronated (Fig. 3). The child evidently suffered much pain as the rigidity increased.

In September the weight was 11 lbs. 10 oz. There was total amaurosis, the appearances at the macula had undergone no change, but optic atrophy was distinct.

On November 11th the weight had fallen to 10 lbs. 4 oz.; nevertheless the child lingered until December 26th, 1894, when it died quietly from exhaustion at the age of 1 year and 8 months, the weight of the body being only 8 lbs. 15 oz.

The history of this case differs from that of the first, in that the boy died before the emaciation and secondary contractions of the muscles had taken place.

Autopsy (an hour and a half after death).—Both fontanelles were closed. On removing the calvaria the

FIG. 3.—This photograph of the girl whose case we have gone into more fully than the former, was taken on September 12th, 1894, and illustrates the characteristic features of an advanced stage of the disease. The child was emaciated, quite unable to sit up, and the different segments of its limbs variously distorted by the spasmodic overaction of muscles, the overextension at the right knee being particularly well shown in the photograph. The cerebral expression is still more marked in this case than in the former.

arachnoid and pia mater were seen to be normal in appearance; they were non-adherent to the brain, and there were no signs of meningitis. The same remarks apply to the membranes of the cord. There was no excess of cerebro-spinal fluid. The distribution of the main vessels at the base and on the upper surface of the brain was normal. The convolutions, fissures, and sulci were well marked, and the latter appeared somewhat wider than normal, but there was no very evident atrophy of the convolutions. The brain weighed 1 lb. 7 oz.; the general consistency was not noticeably altered, and there was no marked vascularity. Portions of the brain, spinal cord, and the sciatic nerve and both eyes were removed and at once placed in Müller's fluid,

which was subsequently changed at regular intervals. The abdominal and thoracic viscera appeared normal to the naked eye.

Microscopical examination.—When sufficiently hardened in Müller's fluid, some portions of the central nervous system and sciatic nerve were prepared for cutting in celloidin in the usual way, and the sections thus obtained were subjected to the influence of various stains, the most important of which were Pal's modification of Weigert's hæmatoxylin stain, picro-carmine, nigrosin, &c. Other portions of the central nervous system and sciatic nerve were cut into thin pieces, after removal from the Müller's fluid, and then placed in Marchi's solution, which consisted of one part of a 1 per cent. solution of osmic acid and two parts of Müller's fluid. The specimens were kept in this fluid, on an average, for about a week, the exact time depending on the size of the particular specimen; and the fluid was changed from time to time as occasion required. On removal from this solution the specimens were prepared in the usual way for cutting in celloidin, and the sections obtained were mounted for examination, no further stain being required as the staining is combined with the process of hardening in Marchi's solution.

In the case of the cerebral and cerebellar cortex, still another method of preparation was adopted: small thin portions of these tissues were transferred from Müller's fluid to Marchi's solution for thirty-six hours, and were then placed in a 0·75 per cent. solution of nitrate of silver for forty-eight hours. The specimens were prepared for cutting in celloidin, and mounted as in the case of those prepared by the Marchi method.

In describing the changes met with on microscopical examination of the various regions, it will, we think, be best to describe the changes as met with in any given part, as revealed by the various methods of staining, rather than to describe under each method of staining the defects met with in this or that region.

Cortex cerebri.—Portions removed from the following

regions were examined after preparation by the various methods that have been detailed.

Superior frontal convolution.
Ascending frontal convolution.
Ascending parietal convolution.
Angular convolution.
Middle temporo-sphenoidal convolution.
Superior occipital convolution.
Cuneate lobule.

It may be said at the outset that no one of these regions was entirely free from some defect, though this was only slight in the case of the superior frontal and middle temporo-sphenoidal convolutions. In the other convolutions examined the changes were very marked, but those in the ascending parietal appeared to be the most pronounced, although the changes met with in the ascending frontal convolution suggested that they were more advanced than in the other convolutions.

The essential change was one of degeneration of the pyramidal cells of the cortex. These cells were to be seen in all stages of degeneration from comparatively slight, in which with neuraxons and dendrons considerably altered the cytoneurons[1] themselves still preserved some of their original shape (see Figs. 4—7), to a stage so pronounced that, as seen in specimens prepared by the silver method, a black irregular mass is the sole representative of what was once a cell, the positions of such black masses in relation to other cytoneurons less altered being often the only reliable evidence that the masses in question represent cells at all.

Between these extremes all degrees of intermediate changes were met with, some cytoneurons being swollen and globose, others partly broken down, but still retaining some evidence of their original shapes, and so on. Groups of degenerated cytoneurons were often met with, and in such groups were often seen side by side cytoneurons in all

[1] In this paper the term "neuron" is used to denote the cell-body with its different processes, "cytoneuron" denotes the cell-body, "neuraxon" the axis-cylinder process, and "dendrons" all other processes of the cell.

stages of degeneration from very slight to a degree amounting to almost complete extinction of the cell.

The changes in the neuraxons and dendrons were most pronounced. Even in those cases where the cytoneurons, though evidently degenerating, still preserved their pyramidal shape, the dendrons were, as a rule, broken off, as were the neuraxons; or the latter, if still continuous with the cytoneurons, showed the presence of the degenerative process most clearly. The beaded appearance due to breaking up of the axis cylinder was most characteristically seen in some instances (see Fig. 5).

Specimens prepared by the Marchi method showed most extensive degeneration of the fibres of the corona radiata, chiefly in connection with the central convolutions. But that all the fibres had not met with this fate was evident on examination of sections prepared by the Pal method, which revealed the existence of a large proportion of healthy nerve-fibres, even in connection with the ascending parietal convolution, where the degenerative processes in the cells were so pronounced.

With so much degeneration present, it will be readily understood that a large amount of free fatty material was distributed throughout the sections. This fatty débris was also taken up by the perivascular lymphatics, some of which were full of this, as is shown in Figs. 8 and 9.

The changes that have been described relate chiefly to the convolutions other than the superior frontal and middle temporo-sphenoidal, in which, as has been explained, the degenerative changes were only slight. Such changes as were met with in these convolutions were of the same nature, but much less marked, isolated degenerated cells being found (see Fig. 7) rather than any clusters of them, as was the rule in connection with the central and other convolutions examined.

The Cerebellum.

Unlike the cerebrum, the cerebellum presented no evidence of degenerative or other change in the cells of

Purkinje or those of the corpus dentatum. Indeed, no structural change could be detected in connection with the organ, apart from certain degenerated fibres met with in its superior peduncles. As only a small piece of the cerebellum was available for examination, there was no possibility of judging of the exact course or distribution of these degenerated fibres in the organ.

The Pons.

The pyramids.—The most striking feature presented by sections stained according to the Pal method was degeneration of the pyramidal fibres (see Figs. 10—13). The appearances presented by such sections, as seen by the unaided eye, suggested complete sclerosis of these tracts of fibres; but on microscopical examination many undegenerated nerve-fibres were seen in these areas of sclerosis. Further, specimens prepared by the Marchi method revealed many nerve-fibres in these areas in a recent state of degeneration, such fibres being stained an intense black by the osmic acid.

The fillet.—This structure also presented evidence of degeneration on both sides; the sclerosis as seen in specimens stained by the Pal method was chiefly obvious in the lateral fillet, while the fibres in a state of recent degeneration, as shown by the Marchi method, were much more numerous in the mesial fillet (see Fig. 14). But in neither the lateral nor the mesial fillet was the extent of degeneration in any way comparable to that seen in the case of the pyramidal fibres.

The descending root of the fifth nerve.—Sections prepared by the Marchi method showed unquestionable evidence of recent degeneration in these tracts (see Fig. 15).

Superior cerebellar peduncles.—No obvious change could be detected in these structures as seen in sections prepared by the Pal method; but in specimens prepared by the Marchi method slight scattered degeneration was evident on both sides. The amount of degeneration was, however, slight, and in no way comparable to that seen in the

descending root of the fifth or in the fillet, which, as has already been said, was in its turn much less in amount than that in the pyramidal tracts.

The posterior longitudinal bundles.—These tracts were practically free from degeneration. The bulk of the nerve-fibres were certainly normal, but here and there a few doubtful spots were seen in specimens prepared by the Marchi method, the exact nature of which it was impossible to be certain about. As was first pointed out by Mott,[1] the only way to be certain as to whether such doubtful spots represent degenerated nerve-fibres or not, is to examine them in longitudinal section, a method which, for obvious reasons, could not be adopted in this case.

The Medulla Oblongata.

The pyramids.—As in the pons so here the most obvious defect was the appearance of the pyramids as seen by the unaided eye in sections prepared by the Pal method. So complete did the sclerosis appear (see Fig. 16) that it would not have been surprising if not a single healthy fibre had been found on microscopical examination. This was not the actual case, however, as many undegenerated fibres were present in both pyramids. Specimens prepared by the Marchi method revealed numerous fibres in a recent state of degeneration also.

The fillet.—The degeneration of the fillet was best seen at its decussation in specimens stained by the Marchi method. The degenerated fibres cut longitudinally could be traced with great exactitude to the nuclei of the posterior columns, in which they all appeared to terminate. Fig. 17 shows these degenerated fibres in their course at the decussation of the fillet. The degeneration was most symmetrical.

The Spinal Cord.

Pyramidal tracts.—Sections prepared by Pal's method showed what appeared to be complete sclerosis of the direct and crossed pyramidal tracts on both sides, as seen

[1] Mott, 'Brain,' 1895, part i, p. 1.

with the unaided eye, and as is shown in Fig. 18, which is a photomicrograph of such a section taken from the cervical region of the spinal cord. On examination under the microscope, however, as in the pyramids at higher levels, so here the pyramidal tracts, both direct and crossed, contained a considerable number of normal nerve-fibres scattered throughout these areas. So, too, in specimens prepared by the Marchi method, a fair number of nerve-fibres in a recent state of degeneration were to be seen. The changes in these tracts, as has just been described, was the same throughout their entire course in the spinal cord.

The Peripheral Nerves.

The sciatic nerve.—The only peripheral nerve from which a piece was obtained for examination was the sciatic. Most careful microscopical examination of sections of this nerve stained by various methods failed to detect any abnormality in its structure. All the nerve-fibres were apparently absolutely intact, and there was no evidence of interstitial change.

Ocular changes.—We are indebted to Mr. Treacher Collins for his kindness in making a microscopic examination of both eyes. The following is his report.

"The optic nerve of one eye was cut longitudinally and of the other transversely. One description of the conditions found will apply equally to the two eyes.

"The optic nerve is much atrophied; there is considerable increase in the amount of fibrous tissue between the bundles of nerve-fibres, and also a large increase in the number of round-cells in the nerve. In one section a considerable collection of round-cells is seen situated between the central vein and artery at the intra-ocular end of the nerve. There is considerable cupping of the optic disc, due to atrophy of the nerve-fibres almost down to the lamina cribrosa, and not to depression backward of that structure. No inflammatory exudation is seen between the dural and pial sheaths of the nerve. The central

artery is full of blood-clot, the central vein is empty; no alteration is seen in the walls of either vessel.

"The choroid in the region of the yellow spot has its vessels dilated, but no inflammatory or other changes are seen in it.

"The retina at the yellow spot has a fold or ruck in it (see Fig. 19), so that it is slightly detached in that region from the choroid. It is there much thickened, due to enlargement of the outer molecular layer, the tissue of which is much spaced out (see Fig. 20), here and there cavities being left; the condition is apparently due to œdema. So far as can be made out, the other layers show no changes. Elsewhere than in the yellow spot the retina appears healthy.

Treatment.—On admission the child was given Potas. Iod. gr. ½ three times a day, which quantity was soon increased to gr. 1 thrice daily, and continued for one month with no apparent ill effect, but without benefit.

On February 1st, 1894, tabloids of cerebrine were administered; at first 1 grain three times daily, afterwards increased to 10 grains in the twenty-four hours, and continued for two months. All active treatment was then discontinued until the end of June, when in consequence of Andriezen's observations[1] on the nature of the pituitary gland, a fresh sheep's gland was obtained daily, finely minced and pounded, and administered each day for six weeks. No further treatment was carried out beyond such general directions as to food and warmth as the wasted condition of the child demanded. None of the measures adopted appeared to have the slightest effect in arresting the gradual progress of the disease.

Case 3.—David R—, brother of the preceding patients, born November, 1894. Was seen for the first and only time on February 20th, 1896, being then fifteen months old.

The mother stated that he was older than the other children before any signs of the disease appeared; in fact,

[1] 'Brit. Med. Journ.,' 1894, vol. i, p. 54.

not until the sixth month was any change noticed, the first sign being the weakness of the back and difficulty in holding his head erect; the enfeeblement subsequently extended to the muscles of the extremities.

When examined, the child lay helpless in bed with its head thrown back, quite unable to move. The forearms were extended, and the hands pronated. If flexed, the arms returned to the extended position.

The legs were extended on the thighs, but the rigidity could be overcome without much force.

The body was wasted. General intelligence was better retained than in the case of the other children, and the child recognised the voices of his parents; but the expression of the face indicated mental enfeeblement, and he frequently laughed without cause.

Hearing was acute; any sudden sound made the child jump violently.

Vision was nearly abolished. Symmetrical changes at the macula similar to those occurring in the other patients were present. There was also distinct optic atrophy.

Dr. F. J. Smith's case.—We are greatly indebted to Dr. Smith for his kindness in allowing us to include in this paper an account of a case of the disease which was under his observation at the London Hospital, and which has not been previously published.

Garvil L—, aged 12 months, the child of healthy parents, both of whom were Jews. There were four other children in the family, all of whom were healthy, and the mother had had no miscarriages.

Nothing abnormal was noticed until the child was three months old, when the parents observed that it was backward as regards mental and bodily development. The child was then taken to the Evelina Hospital, and from there it was referred to Moorfields, where the parents were advised to take it to a general hospital. It was admitted into the London Hospital on February 17th, 1894, when its condition was as follows:—It cried vigorously when disturbed,

moved its limbs freely when attempts were made to examine the fundi; the movements of the arms and legs seemed perfect in execution, though the child did not appear to move them voluntarily except to put its fingers in its mouth. It was quite unable to sit up, and the muscles of the arms and legs were flabby. There was inclination to talipes varus of the left foot.

The superficial plantar reflexes were not brisk, but definite; both knee-jerks were glib.

The fontanelles were closed; the forehead was not particularly square or prominent. The lower median incisor teeth were just protruding through the gums. There was no particular enlargement of the wrists, and the tibiæ, though bowed outwards, especially the right, presented no enlargement of the epiphyses. The rib cartilages were not enlarged.

There was no enlargement of the liver or spleen, nor was there any enlargement of the glands in the neck or groin.

Ocular changes were present, and consisted in a whitish-grey appearance at each yellow-spot region, in the centre of which area was a red spot. The fundus was otherwise normal.

The child gradually wasted, and became progressively weaker. A week after admission difficulty of swallowing became apparent, and steadily increased. No other change was noted up to the time of death, which took place on April 11th, 1894, nearly two months after admission to the hospital.

No special treatment was adopted. A post-mortem examination was not allowed.

Characteristic Features of the Disease.

Etiology.—The disease occurs in both male and female children, and of twenty-three cases recorded, including those which form the subject of this communication, eight have been in boys, eleven in girls, and in four the sex is not stated. No distinct exciting cause can be assigned.

It has no apparent relation to syphilis, consanguinity of marriage, or any of the usual hereditary diatheses.

Racial peculiarity appears to have some influence; in the published instances of the disease in which the nationality has been stated, including all the cases occurring in this country, the children have been Jews.

More than one child of the same parents is usually attacked, but no regularity is observed in the order in which this takes place. It may be the earlier or later children, or every other child, while the other members of the family are quite healthy.

Symptoms and progress.—For convenience of description the symptoms and progress of the disease may be considered as they occur in three stages.

The first stage.—An infant, the subject of this disease, is born at the full term of gestation, and may be well formed and developed, differing in no outward respect from a healthy child, until about the completion of the third month. At this time some weakness of the muscles of the back and neck is observed, and often a suspicion that the child sees imperfectly is entertained. Should the eyes be examined with the ophthalmoscope about the fourth or fifth month, definite and characteristic changes will be discovered in the region of the macula lutea. These will be described more in detail later.

The second stage.—The child is now unable to sit up, its head falls backwards if unsupported; when lying on its back it is unable to turn on to either side. Objects placed in its hands are grasped but feebly, and soon dropped. It generally is apathetic, taking no notice of surrounding objects, and the face bears an expression of mental enfeeblement. Vision is reduced to perception of light, but the sense of hearing is acute, and remains so during life, any sudden sound causing the child to start. The sense of taste is also preserved.

The third stage.—Atrophy of the enfeebled muscles ensues, and soon those of the whole body are involved. Emaciation progresses and becomes most marked. The

deep reflexes are exaggerated, and still later in the course of the disease, rigidity of the extremities and retraction of the head become prominent features; occasional spasmodic contractions cause the child to start and cry from pain. Convulsions have been noted in one or two instances during the course of the disease, but they would appear to be an accidental accompaniment, and are at all events not the rule.

The temperature remains normal throughout the course of the disease. The heart, lungs, and abdominal viscera are also normal.

The ocular symptoms.—The ocular symptoms, which are an early and we believe an absolutely diagnostic sign of the disease, consist in symmetrical changes at the macula lutea, in which situation, covering a space nearly twice the size of the optic disc, is a whitish-grey patch, only slightly raised above the general surface of the retina, somewhat oval in shape (the axis being horizontal) with softened edges. A few retinal vessels are visible on it at the periphery. In the centre of the patch is seen the fovea centralis as a dark cherry-red spot (see Fig. 21). There is no other opacity of the fundus, and one is forcibly reminded of the appearances seen in embolism of the central artery of the retina. In the early months the optic papilla shows no decided changes, and the child can perceive light. Later on there is definite optic atrophy (see Fig. 21), and total amaurosis. It is to be noted, however, that the changes at the macula from the date of their appearance until the close of life remain unaltered. That they are not congenital is proved by an observation of Mr. Tay's ('Trans. Ophthal. Soc.,' vol. iv), and also by the condition found in our second case.

The duration of life.—The duration of life varies from one and a half to two and a half years, but is usually less than two years. All the subjects of this disease are known to have died except two, and they were becoming worse when last seen. It can be well understood that the duration of life must largely depend on the care and attention

bestowed upon the child in checking any intercurrent disorder; but apart from these causes, death is sometimes unexpectedly sudden.

Morbid Anatomy.

Central nervous system.—Degeneration of the neurons of the cerebral cortex is the fundamental change in these cases. Further, all the evidence points to this change being a primary one of the nerve elements, and in no way secondary to any inflammatory or other process. The appearances met with also indicate a progressive change; even in those parts where it is most advanced there is abundant evidence of the progressive character of the disease as shown by the different degrees of degeneration of the pyramidal cells met with in the same section.

With such changes in the cortex it is not surprising that there should be degeneration of the fibres of the corona radiata, and of the pyramidal tracts throughout their whole course through the pons, medulla, and spinal cord.

The other tracts which we found degenerated were the fillet, the descending root of the fifth nerve to a less degree, and the superior cerebellar peduncles still less; all these structures being affected symmetrically on the two sides.

Eyes.—The retina at the yellow spot is much thickened, this being due to enlargement of the outer molecular layer, the tissue of which is spaced out, the most marked changes occurring in the neighbourhood of the fovea, and becoming less evident towards the periphery of the affected area. The other layers show no changes, and the retina in parts other than the yellow-spot region is healthy.

It seems highly probable that much of the prominence of the macula region of our second case, as seen in the microscopic section, is the result of accidental circumstances connected with the process of preparation of the tissue for microscopic examination. This is suggested by the appearance, by the existence of a similar though much smaller fold of the retina outside the macula area (see Fig. 19), and by the fact that such an obvious elevation could hardly be

overlooked in an ophthalmoscopic examination, whereas neither by ourselves nor by others has any marked swelling of the area been noted during life. There is, however, apart from any accidental circumstance, an increase in the width of the outer molecular layer in the region of the macula.

The optic nerve is atrophied with increase of interstitial connective tissue, and large increase in the number of round-cells in the nerve. There is considerable cupping of the optic disc, the result of atrophy of the nerve-fibres. There is no inflammatory exudation between the dural and pial sheaths of the nerve.

Pathology.

Central nervous system.—Apart from the clinical evidence that the disease is not congenital, but develops after about the third month of extra-uterine life, the changes met with in the central nervous system preclude the possibility of any such view being entertained. In all the parts of the central nervous system examined in our cases there was nowhere the slightest indication of any congenital defect. All the structures appeared to have been normally developed, and the degenerative changes met with were certainly occurring in normally developed structures. As has been already said, those pyramidal cells in the cerebral cortex in which the changes were least marked appeared of almost normal shapes and sizes, and their arrangement was regular and in every way compatible with a normal state of things prior to the onset of the degeneration in them.

The condition of the pyramidal tract as seen by the unaided eye in specimens prepared by the Pal method strongly suggested a complete absence of any myelinated fibres in these tracts, so that it at once seemed likely that the cortical changes reached an advanced stage early enough to preclude the possibility of the pyramidal fibres becoming myelinated at all. That this view could not be wholly correct was, however, quickly evident on submitting the specimens to microscopical examination, for it then became

clear that many myelinated fibres existed in the pyramidal tracts. Further, the fact that specimens prepared by the Marchi method showed recent degeneration, a method whose reaction depends on the disintegration of the myelin, is additional proof that this view cannot be maintained in its entirety. At the same time it is impossible to deny that some of the pyramidal cells of the cortex may have undergone degeneration early enough to exclude some of the pyramidal fibres from ever becoming myelinated.

The occurrence of changes in the pyramidal tracts in association with the degenerative changes of the pyramidal cells of the cortex cerebri leave very little doubt that the former is dependent on the latter, though the advanced state of degeneration of the pyramidal tracts suggests the possibility that these changes may have preceded those met with in the cerebral cortex. There are, however, no grounds for assuming that the morbid condition is primarily one of the pyramidal tracts which later involves the cortex, if we examine the evidence supplied by the clinical history of the disease, for the cerebral symptoms preceded all those that could be ascribed to sclerosis of the pyramidal tracts.

The degeneration of the direct pyramidal tracts corresponds so exactly in every particular with that met with in the crossed pyramidal tracts that these cases afford important proof that Boyce's observation,[1] that in the cat all the pyramidal fibres decussate and leave no direct pyramidal tract, is not true of man.

In the absence of any detectable lesion of the posterior column nuclei, it must be granted that the change met with in the fillet is a descending degeneration.[2] But in spite of the marked changes in the cerebral cortex the case cannot be claimed as one showing that fibres pass downward from the cerebral cortex in the fillet directly to the posterior column nuclei, as the basal ganglia were not obtained for examination. All that the case proves in this

[1] Boyce, 'Phil. Trans. Roy. Soc.,' vol. 186, 1895, B, p. 321.

[2] Cf. Monakow, 'Neurol. Centralblatt,' 1885, p. 65; and Flechsig and Hösel, 'Archiv f. Psychiatrie,' Bd. xxiv, Heft 8.

respect, then, is that fibres do certainly appear to degenerate downward or caudalward in the fillet, but as to whether such fibres come directly from the cerebral cortex or whether from the basal ganglia must be left an open question.

The same must be said of the degeneration met with in the descending root of the fifth nerve, and, in the absence of any primary changes in the cerebellum, of the degenerated fibres seen in the superior cerebellar peduncles.

Eyes.—The precise relationship of the ocular changes to those met with in the central nervous system is not very evident. The statement, however, applies more to the changes at the macula than to the atrophy of the optic nerve, for this latter condition is commonly associated with certain degenerative diseases of the central nervous system. In spite of Mr. Waren Tay's experience in the early stages of one case, the atrophy must, we think, be looked on as a primary one and not secondary to neuritis; it certainly was so in our own cases, and it has all the characters of a primary rather than of a post-neuritic atrophy. With regard to the changes at the macula, it is difficult to understand why the outer molecular layer should especially be affected. It is just possible that the changes are due primarily to a degeneration of the ganglion cells of the retina similar to that met with in the pyramidal cells of the cerebral cortex, and that the limited ophthalmoscopic appearance is partly due to the much greater abundance of these cells in the macular region; but of this we have no evidence, as unfortunately the specimens were not prepared by methods specially calculated to reveal the existence of such changes. One thing is, however, quite certain, and that is that the changes at the macula are not of embolic origin.

Doubtful as is the nature of the relationship between the ocular changes and those of the central nervous system, the relationship of the ocular changes to each other is no less obscure: whether the optic atrophy is secondary to and dependent on the changes at the macula; or whether, as seems more probable to us, they are both dependent on a common cause related to the changes met with in

the cerebral cortex, must, for the present, be left undecided.

Treatment.—In view of our imperfect knowledge of the primary cause of this disease, any treatment adopted must be more or less experimental. We, at any rate, now know the degenerative changes which are in progress, and must endeavour to combat them. We also know that if one member of the family has been attacked, some other children of the same family will almost certainly suffer. Can we therefore prevent its occurrence by the administration of any remedies to the mother when *enceinte ?* The only attempt which we have made in this direction was by giving the mother Potass. Iodidi gr. v thrice daily during the whole period of two pregnancies ; but the result was negative, as one child was healthy but the other has been attacked.

For the same reason it would seem advisable that where the one child is known to have suffered, subsequent infants should be weaned from the time of birth. We are not aware whether this has been carried out ; our own patients were nursed by their mother.

Addendum.

When our paper was presented to the Society in March, 1896, the fifth child of the family, though affected, was still alive, and the sixth child when examined in February, 1896, appeared healthy. The sixth child has since become affected, while the fifth child died on May 6th, 1896, and a microscopical examination of the central nervous system has been made. We have, therefore, altered the account of the history of the family, which is to be found at the commencement of the paper, in accordance with the state of the family now as opposed to the condition of things which existed last March.

We now propose to add the briefest possible clinical report of the terminal stages of the illness of the fifth child (Case 3 in the paper), to note the date when the

disease was detected in the sixth child of the family, and to give a short account of the autopsy and subsequent microscopical examination of the nervous system in Case 3.

David R— was first seen when three months old, at which time he presented no evidence of the disease. The patient was not seen again until March 8th, 1896, when he was admitted into the Children's Hospital at Nottingham, being then fifteen months old. The symptoms, both general and ocular, were similar to those already described, but from the mother's statement they would appear to have been later in commencing, viz. at the sixth month.

The child was fairly nourished, and weighed 14½ lbs. Paresis of the limbs existed, and was associated with occasional rigidity, but there was no permanent flexion or extension consequent on muscular spasm.

The patient remained in much the same condition until four days before death, when he gradually became unconscious, and died on May 6th, 1896. There were no convulsions, nor was there any rise of temperature.

Autopsy.—An examination of the head was made five and a half hours after death. There was no thickening, opacity, or adhesions of any of the cerebral membranes. The brain weighed 2 lbs. 2 oz., was firm in consistence, and the sulci were compressed. There was no excess of cerebro-spinal fluid. Portions of different regions of the cerebral cortex, the basal ganglia, pons, medulla, upper part of spinal cord, and cerebellum, together with the posterior halves of the eyes, were at once placed in Müller's fluid for preservation and subsequent microscopical examination.

Microscopical Examination.

Cortex cerebri.—Extensive degeneration of the pyramidal cells of the cortex was found, but the condition was evidently less advanced than in Case 2, as there were no evidences of fatty disintegration of the cells, and the perivascular lymphatics did not contain fatty débris, as

was the case in the other patient's brain. Although not so advanced, the changes were none the less pronounced, as was best shown by specimens prepared by Nissl's method. The pyramidal cells were variously altered in shape, the majority being so distended as to have entirely lost their pyramidal shape, and to have become balloon-shaped (see Fig. 22); others, while distended, preserved some slight traces of their former pyramidal shape; while some cytoneurons showed evidences of commencing disintegration at parts. The granules of the cells were in some instances collected around the nucleus, while in the less altered cytoneurons fine granules could still be seen scattered in their interior, but all coarse granules had disappeared. Some of the cells appeared to have entirely lost their granules, a process of vacuolation of the cytoneuron having taken place; and in others the granules appeared to have run together more or less at the periphery of the cell. Many phagocytes lying in close relationship to the pyramidal cells contained deeply stained granules, while others of these phagocytes were to be seen round the vessels of the cortex. The nerve-fibres were degenerated, and the general appearance presented by the meshwork of interlacing fibres suggested an abnormal spacing out and separation of the various elements of the cortex, such as might reasonably be supposed to have been brought about by an œdematous condition of these parts.

Basal ganglia.—Nothing abnormal could be detected in connection with the basal ganglia, but the fibres of the internal capsule were degenerated.

Pons.—Well-marked degeneration of the pyramidal fibres was traced through the pons, both as shown by a modification of Pal's method, and as seen in specimens prepared by the Marchi method. Degeneration of the fillet could also be traced through the pons.

Medulla oblongata.—The degeneration of the pyramids was well seen throughout the medulla, and the degeneration of the fillet was strikingly evident at the decussation of this structure, its recently degenerated fibres, stained

by the Marchi method, being seen in longitudinal section, passing between the interolivary layer and the posterior column nuclei. The cells of the posterior column nuclei showed no evidence of degeneration.

Spinal cord.—The portion of the cervical region of the spinal cord which was available for examination showed well-marked degeneration of both crossed and direct pyramidal tracts. All other tracts of the spinal cord in this region were intact, and no alteration in the grey matter could be detected.

Optic nerves.—There was well-marked atrophy of the optic nerves.

R—, a boy aged 8 months, another member of the same family, was kindly examined for us by Mr. Treacher Collins and Mr. Tay, at Moorfields Hospital, on July 23rd, 1896, when the characteristic changes were found at each macula.[1]

Remarks.—It is interesting to find that the changes met with in the central nervous system of Case 3 so closely correspond to those that were met with in connection with Case 2. Of still greater interest, however, is the fact that Case 3 died in an earlier stage of the disease than did Case 2, and that the changes met with on microscopical examination of the cortex cerebri in Case 3 were correspondingly representative of an earlier stage in the process of cerebral degeneration than those met with in connection with Case 2.

The possibility that many of the pyramidal fibres may never have become myelinated is still more forcibly suggested to us by the last case examined than by the former one, in that with more recent changes in the cerebral cortex, the apparent sclerosis of the pyramidal tracts in the pons, medulla, and spinal cord is extensive.

[1] On January 12th, 1897, there was some inability to hold up the head, and to sit up unsupported. Objects were grasped feebly. The limb muscles were flabby, but responded normally to the faradic and galvanic currents. There was moderate flexor spasm of the hands and feet. The knee-jerks were present, but not exaggerated. Cutaneous sensibility appeared to be preserved.

In that, so far as has been discovered, the lesion is a purely cortical one, the degeneration of the fillet is of interest, the evidence supplied by Cases 2 and 3 supporting the view that a cortical fillet exists, and that it is capable of degenerating downwards. Certain it is that in neither case could any lesion of the posterior column nuclei be discovered, and that though in Case 2 the basal ganglia were not examined, an examination of these structures in Case 3 showed no change.

Bibliography.

1. Waren Tay, 'Trans. Ophth. Soc.,' 1881, vol. i, p. 56; vol. iv, p. 158.

2. Goldzicher, of Buda-Pesth, 'Hirschberg's Centralbl.,' 1885, p. 219.

3. Magnus, of Breslau, 'Zehenher's Klinische für Augenheilkunde,' 1885, vol. xxiii, p. 42.

4. Knapp, of New York, 'Trans. of Heidelberg Ophth. Soc.,' 1885, p. 217.

5. Wadsworth (O. F.), of Boston, U.S.A., 'Trans. American Ophth. Soc.,' 1887, vol. iv, p. 572.

6. Sachs (B.), of New York, 'Journ. of Nervous and Mental Diseases,' New York, September, 1887.

7. Hirschberg, of Berlin, 'Hirschberg's Centralbl.,' 1888, p. 14.

8. Kingdon, 'Trans. Ophth. Soc.,' 1892, vol. xii, p. 125.

9. Carter, of New York, 'Archives of Ophth.,' 1894, vol. xxiii, p. 126.

10. Sachs, 'New York Med. Journ.,' May 30th, 1896.

(For report of the discussion on this paper, see 'Proceedings of the Royal Medical and Chirurgical Society,' Third Series, vol. ix, p. 37.)

DESCRIPTION OF PLATE XVI.

Infantile Cerebral Degeneration with Symmetrical Changes at the Macula (E. C. KINGDON and J. S. RISIEN RUSSELL).

FIG. 4.—A photomicrograph showing degenerated pyramidal cells from the ascending frontal convolution. Most of the cytoneurons[1] have been destroyed to a degree past recognition, but there are three on the right side of the figure which have preserved some of the characters by which they can be recognised as cells, though that farthest to the right is almost beyond this stage.

FIG. 5.—In this figure also three cytoneurons can still be recognised as such—two towards the middle line in the lower half of the photograph, and the third to the left of these and at a higher level. The latter shows the broken-up, beaded appearance of its neuraxon, a condition far better seen under the microscope than it has been possible to reproduce in the photomicrograph, which was taken from a specimen of the ascending parietal convolution.

FIG. 6.—Only one cytoneuron near the centre of the photograph has escaped alteration beyond recognition; its dendrons are broken off short, and but a slender remnant of its neuraxon is still to be seen. There are other possible cells in this figure, but they have reached a stage of disintegration which makes it impossible for a positive opinion to be expressed about them.

FIG. 7.—This is an example of an isolated degenerated cytoneuron. Its dendrons are broken off short, but a considerable length of the neuraxon is still connected with the degenerated cytoneuron.

FIG. 8.—This photomicrograph shows a blood-vessel in the middle of the field with its perivascular lymphatic space full of fatty débris stained black by osmic acid.

FIG. 9.—This figure represents another vessel seen under a higher power of the microscope than the last. The outline of the vessel can be well seen, with the globules of fatty débris in its perivascular lymphatic space.

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[1] "Neuron" = the cell-body with its different processes; "cytoneuron" = the cell-body; "neuraxon" = the axis-cylinder process; and "dendrons" = all the other processes of the cell.

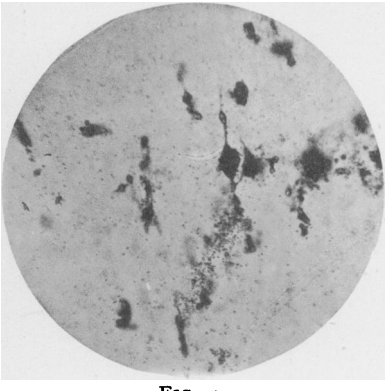

FIG. 4.

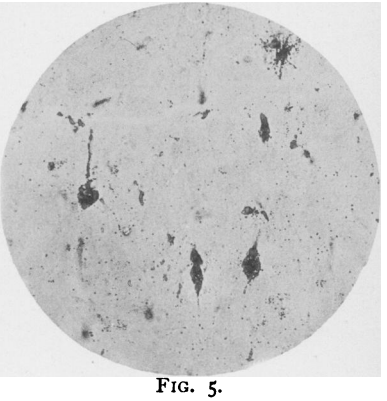

FIG. 5.

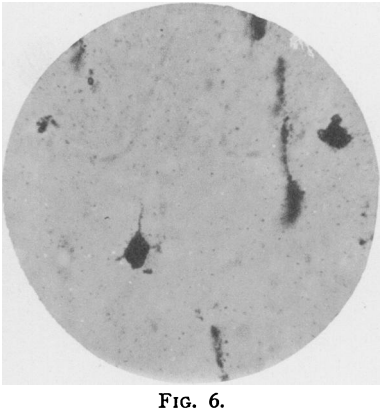

FIG. 6.

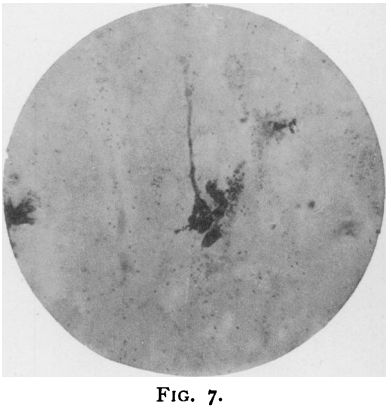

FIG. 7.

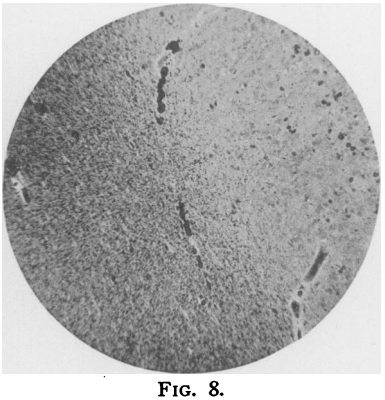

FIG. 8.

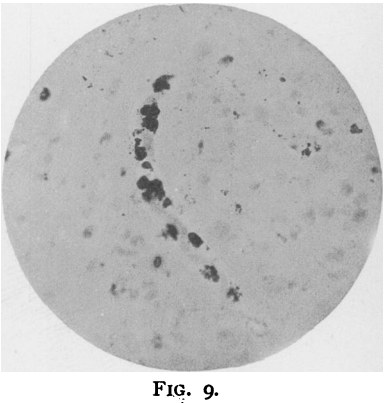

FIG. 9.

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DESCRIPTION OF PLATE XVII.

Infantile Cerebral Degeneration with Symmetrical Changes at the Macula (E. C. KINGDON and J. S. RISIEN RUSSELL).

FIGS. 10, 11, 12, and 13.—In all these photographs, which have been taken from specimens stained by the Pal method, the sclerosis of the pyramidal fibres is evident; and in Figs. 10 and 11 some sclerosis of the lateral fillet can also be made out.

FIG. 16.—What appears to be complete sclerosis of the pyramids in the medulla oblongata is shown in this photograph of a specimen stained by the Pal method.

FIG. 18.—The sclerosis of both direct and crossed pyramidal tracts, as seen in transverse section in the cervical region of the spinal cord, is well shown in the photograph, also taken from a specimen stained by the Pal method.

FIG. 10.

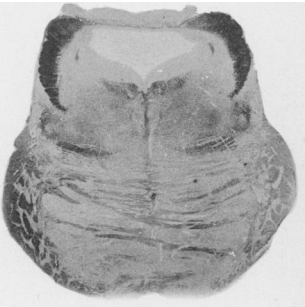

FIG. 11.

FIG. 12.

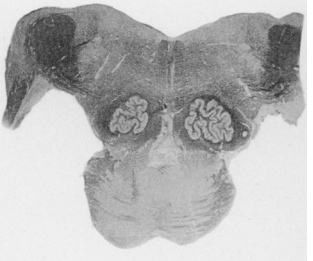

FIG. 13.

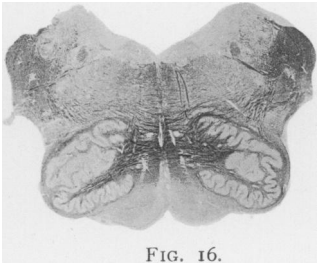

FIG. 16.

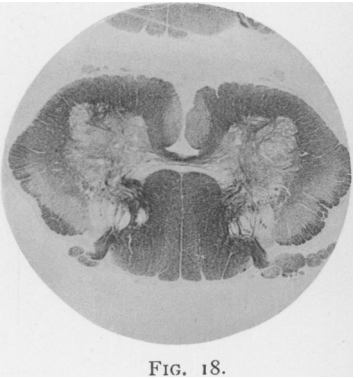

FIG. 18.

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DESCRIPTION OF PLATE XVIII.

Infantile Cerebral Degeneration with Symmetrical Changes at the Macula (E. C. KINGDON and J. S. RISIEN RUSSELL).

FIG. 14.—A portion of the mesial fillet is seen in this photomicrograph, with scattered degenerated fibres stained black by the Marchi method, and seen as black dots on transverse section.

FIG. 15.—The black dots in the centre of this figure represent degenerated fibres in the descending root of the fifth nerve as seen on transverse section in a specimen stained by the Marchi method.

FIG. 17.—The degenerated fibres of the fillet are well seen, many of them in longitudinal section at the decussation of the fillet. The opposite course of the fibres from the two sides as they cross in the middle line can be readily made out.

FIG. 22.—The altered characters of the cytoneurons of the cortex of the ascending parietal convolution in Case 3.

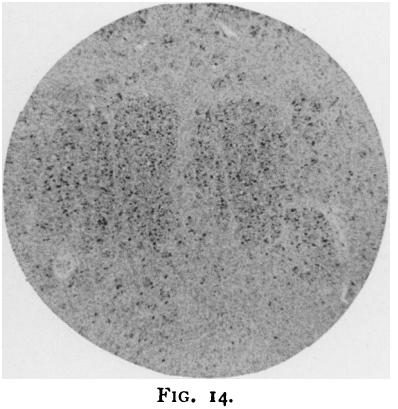

FIG. 14.

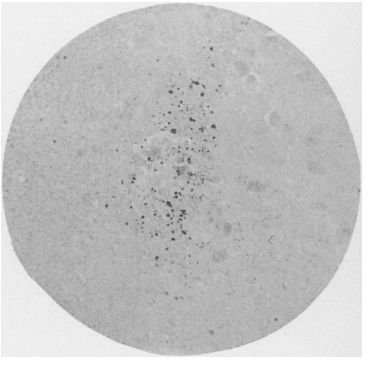

FIG. 15.

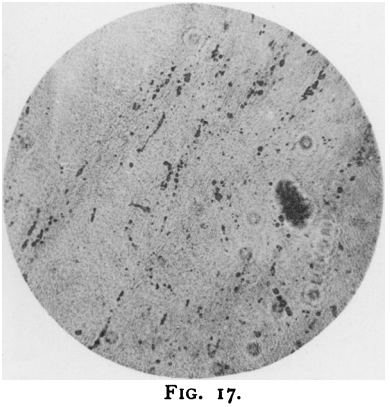

FIG. 17.

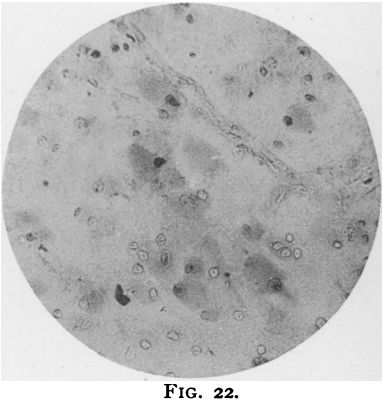

FIG. 22.

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DESCRIPTION OF PLATE XIX.

Infantile Cerebral Degeneration with Symmetrical Changes at the Macula (E. C. KINGDON and J. S. RISIEN RUSSELL).

FIG. 19.—The fold in the macula region which was met with on microscopical examination in Case 2 is shown in this photomicrograph.

FIG. 20.—A portion of the retina in the macula region under a higher power of the microscope than the last; it shows the increase in depth of the outer molecular layer.

FIG. 21.—The characteristic appearances in the macular region, as seen with the ophthalmoscope during life, are indicated in this figure, in which the optic atrophy is also represented.

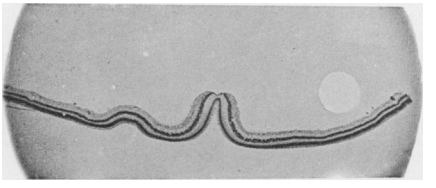

FIG. 19.

FIG. 20.

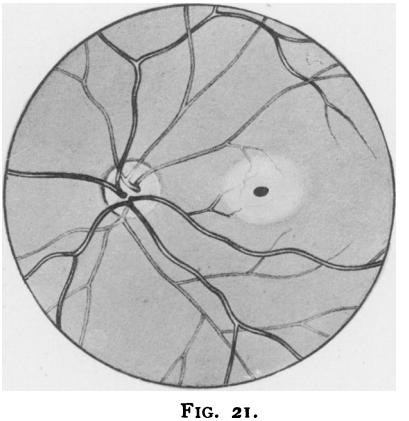

FIG. 21.

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