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Sigm. Freud (*Nothnagel Spec. Pathol. u. Therap.*, Vol. ix., 2d Part, 2d Division, Page 255), in a special chapter of his work on infantile cerebral paralysis, discusses the family and hereditary forms of the latter affection. They differ in this, that sometimes more than one case will make its appearance in a single generation; in other instances, subsequent generations may exhibit the very identical or similar morbid processes. He feels justified in proposing the following classification of all the cases which may come under this head:

1st. Cerebral paralysis may occur in more than one member of a family. The cases are identical or similar in different persons and stages. Strabismus or spastic hemiplegia may be met with.

2d. Typical diplegiæ are met with in the same family or in consecutive families.

3d. Such cases as may be observed under the same circumstances, and may be defined as typical diplegia, though they differ from it to a certain extent.

4th. Such family disorders of infancy as are markedly different from infantile cerebral paralysis.

5th. The family—or hereditary—affections of later life.

Feeble intellects, with progressive muscular atrophy, were met with by Hofmann in four brothers and sisters; atrophic bulbar paralysis has been observed in families, and under hereditary influences; relapses of spinal paralysis—after recovery was complete—have also been noticed. Then there are the various forms of Little's disease—that is, paralytic conditions dating from protracted labors. There is Friedreich's disease,

*Read before the American Pediatric Society, Cincinnati, June 2, 1898.

with tremor, oscillating gait, which is not influenced by closing the eyes, with nystagmus, and slow and monotonous articulation, but with no spasm, with extinction of patellar reflexes, with little disturbance of sensation, and with deformed foot and scoliotic spine; finally Marie's "hérédo-ataxie cérébelleuse," also (like the former) with tremor, oscillating gait, which is not influenced by closing the eyes, with nystagmus, and slow and monotonous articulation; but (to distinguish it from Friedreich's disease) with no deformities, increased reflexes, occasional contractions, and more disturbed sensation and affection of the eye muscles. All of these show the possible varieties, differences and degrees. In only a few the anatomical diagnosis can be made so correctly, as, for instance, in Friedreich's disease, which consists in a degeneration of the long spinal nerves and in smallness of the cord; or that of Marie's, in which the cerebellum is found to be reduced in size.

Under No. 2 Freud subsumes the cases of amaurotic family idiocy—a preliminary title given by Dr. B. Sachs, of New York, to a limited number of cases of a peculiar nature, which will be described hereafter. It appears to me that the classification of Dr. Freud is too indefinite to be accepted. If anything, it shows that the varieties, anomalies and alterations, both anatomical and clinical, in morbid conditions of the nervous system, which, result in or are complicated with idiocy, are too manifold, or, in many cases, too closely related to each other to permit of iron-clad boundary lines.

"Amaurotic family idiocy" is certainly exceptional in this respect, that it permits of a ready clinical diagnosis. Whether the anatomical lesions underlying all the cases, or their embryological development are identical, remains to be seen.

Dora R. was presented at my college clinic four months ago. Through a mistake of mine, or that of an assistant—certainly not through that of the gentleman who examined her eyes for him—I gained the impression that the retina showed either a plain bilateral hemorrhage or a bilateral glioma. The brief exhibition of the infant before my class, undertaken without further examination and without a history, was made for the sole purpose of presenting what I thought to be a fair illustration of Locke's dictum: *Nihil est in intellectu quod non antea fuerit in sensu*, "the road to intellect goes through the senses." It appeared to me that the defective intellectual development of the

child might be due to her increasing blindness and to the corresponding lack of sensory food. When, however, the defective muscular innervation was noticed, and when Dr. Gruening saw the child and corrected my erroneous opinion in regard to the condition of the retina, the case looked different.

She was one year old, and the fourth child of healthy, not neurotic, not syphilitic, not alcoholic, Semitic parents. No hereditary taint known. Their first child was six, the second four, the third three years old; all were in perfect health. Labor was easy; no asphyxia; no convulsion. Infant was nursed by her mother until the present time, with the exception of additional meat-soup and oatmeal decoctions during the last month; was considered normal by the mother during the first few months; she did not remember, however, when the baby smiled the first time. The first tooth, a lower incisor, appeared at ten months; three upper came since; four more teeth were protruding. The fontanelle was about to close; no pulsation was felt through it. Circumference of the head, 40½ centim.; forehead rather narrow.

The infant never was able to sit alone or to hold up her head. When she was seven months old she did not notice so much or play so well as formerly; gave but little attention, cried but seldom, and slept a great deal. Some months ago spastic contraction of the upper extremities was observed repeatedly. Mother believed that during these last three months the infant noticed more, again. She felt certain that her eyes followed a light occasionally, and, at times, persons.

But her intellect was feeble when presented; she did not appear to notice, and she did not smile, except occasionally, in a listless manner. There were rhachitical curvatures with convexity outwards; the epiphyses of the radius and ulna were rather enlarged, but other symptoms of rickets were absent. There was no Harrison's groove, there was no excessive perspiration, and no falling out of hair on the occiput. The fontanelle has been mentioned as nearly closed, rather earlier than usual; but there was no hyperostosis nor anything pointing to premature ossification; no constipation. I mention the latter circumstance because the involuntary muscles, so often and badly affected in rhachitis, did not suffer here like the voluntary. These, all over the body, were flabby and inactive. Her motions were listless; her head found no muscular support; muscular

contraction under the influence of electricity was insufficient. The response to faradic irritation was diminished and quite slow; a rather strong current exhibited a contraction after from one to two seconds only. Galvanic irritability was also diminished, to a certain extent the lower extremities, much more so the upper; decided reaction of degeneration. Patella reflexes were rather normal, perhaps a little exaggerated; no ancle clonus. There was some slight dulness (normal) over the manubrium sterni. Thyroid seemed normal in extent and consistency. Pupils did not, or but very slightly, respond to light, either direct or reflected; no nystagmus, no strabismus, no convulsions; heart, lungs and kidneys were normal. The shape and consistency of the eye were normal. There was a white patch with a red centre, instead of the macula lutea and beyond it; in its centre was a depressed spot. The optic disk was pale and gray.

This degeneration is the same which has been described in all the cases hitherto observed, the first time by Waren Tay and Kingdon (in the former's first cases) as early as 1881.* The fundus was found normal until after the third month; it was then that the first haziness began to show itself in the macular region. The condition became worse about the fifth and sixth months, while vision grew worse gradually, until total blindness set in.

SECOND CASE.—Lina K. was presented in my office on the 23d day of September, 1897. Father and mother were each twenty-six years of age, both of the Semitic race, and emigrated from Russian Poland. They had another girl that died at the age of one-and-a-half years, two years previously. She never was strong enough to sit up or to hold her head. She was nursed until she was fourteen months old. At that time she had her first tooth; four when she died. She had her first convulsion with nine months. During the attack she appeared to be breathless; the eyes were turned up; other spasms occurred several times a day, both in the upper and lower extremities until she died. The face began to participate in these

*Since the subject has been discussed, amongst others, by Goldzieher, Magnus and Knapp in 1885; by Wadsworth in 1887; by Sachs in 1887, 1896 and 1898; by Hirschberg in 1888; by Kingdon in 1892; by Carter in 1894, and lately by E. C. Kingdon and J. S. Risien Russell in the (1897) eightieth volume of the *Med. Chir. Trans.* ("Infantile Cerebral Degeneration with Symmetrical Changes at the Macula").

attacks when she was fifteen months old. When Lina K., was first presented, there were no very prominent symptoms, except listlessness and muscular weakness; no convulsions. The eyes certainly followed the watch. The erroneous diagnosis of rhachitical feebleness, "pseudo-paralysis," was made, and elixir of phosphorus and the syrup of iodide of iron were ordered. On February 23d she was next seen in my service at the Vanderbilt Clinic when fourteen months old. She still appeared to follow the watch, sometimes listlessly; her hearing was good; the repeater near her ear made her start, and dilated the rather large pupils. The eyes were mostly turned upwards; the head hung back; muscular action was very slow everywhere; she never held anything in her hands. The bowels were costive, and moved hard and sluggishly only once in two days, after enemata. The left leg required a continuous current of 3, the right of 7½ milliampères for muscular contraction; the interrupted current had to be quite strong to accomplish that. There was no reaction of degeneration. For several months past she had convulsions in both arms, hands, legs and feet; convulsions and apnœa appeared to come together with pallor; the attack lasted "a few minutes," and occurred first but three or four times a week, but lately as many times during the day; also in the night. Some were accompanied with laryngismus stridulus; if they were tonic, they were followed by a tearless cry. The mother said the infant smiled when talked to, an assertion which could not be verified. Respiration was shallow, pulse 132 and regular. Fontanelle was still open. When the mouth was opened, its right angle was slightly drawn up. The characteristic change of the retina and macula lutea were looked after, and found by Dr. J. Herbert Claiborne.

A brother of the above patient was, at my request, sent to me by Dr. John Huber. He was then four weeks old, May 28, 1898. Dr. R. O. Born examined the eyes for me on the same day, and reported them to be normal, so far.

THIRD CASE.—G., female, was sent by Dr. Michaelis on April 19, 1898. She was born July 30th, 1897, after a normal labor, and with only a moment's "suspended animation." She was breast-fed. Two months ago, so the mother reported, the infant could not yet sit up. The only apparent disturbance of her health was a bronchitis from which she had suffered six weeks ago. Reflexes were normal; pupils of normal infant size (rather large)

and equal; intellect and muscles certainly feeble. The parents —Semitic—had been married seven years before this first child was born. No miscarriages, no syphilis, some tuberculosis in the father's family. Dr. R. O. Born, whom I requested to examine the eyes for me, reported the presence of the characteristic change in the macula lutea, with no atrophy of the fundus as yet.

While these cases are presented, they are not expected to be utilized for a lengthy review of the subject; for there is a very concise story of what is known of the subject by Dr. Sachs in the third number of the *D. Med. Woch.* of this year. Inclusive of Waren Tay's first three cases, all occurring in the same family, and terminating fatally before the end of the second year, altogether twenty-seven have been published. In all of them there were the same symmetrical changes in the macula lutea, *viz.:* the white, somewhat spherical spot, with a brownish red centre, similar to what is seen in embolism of the central artery, with gradual atrophy of the papillæ, which, in 1885, were studied in our country by Knapp and by Wadsworth; the same lack of innervation as shown by weakness of intellect and of muscles, the same connection first pointed out by Kingdon (Trans. Ophth. So., xii.) of the intellectual deficiency with the characteristic eye changes, and the slow but sure increase of the symptoms. It matters little, and depends greatly on the individual powers or opportunities to observe the progress of such a case, whether there is a little more or less rolling of the eye, or increasing indolence, or reflex anomalies. The general progress and the end have been the same, *viz.:* the blindness and idiocy became complete, nutrition was impaired (marasmus is often mentioned), and a fatal termination completed the history of the cases before the end of the second year. Dr. B. Sachs observed a single case up to the sixth year. In another single case Koller found the eye symptoms to be rather late compared with the intellectual defects, and Higier the retinal atrophy more pronounced than the spot on the macula lutea.

In one of the three cases described by Kingdon and Russell in the eightieth volume of the *Med. Chir. Trans.* of 1897 there was a marked adductor spasm of the lower extremities; in another various distortions by the overaction of muscles, and overextension at the right knee. Such variations—even the oc-

casional aural disturbances from hyperacusis to dull hearing—establish no essential difference in the general symptomatology.*

Our anatomical knowledge of the pathological changes underlying these uniform vital changes left, until a short time ago, and still leaves, much to be desired. In one of the four older autopsies the arachnoid and pia were found thickened, the cortex hard, the cerebral fissures strongly marked, the sulcus Rolando and the fissure of Sylvius confluent (always a low form of development), and the island of Reil uncovered. The pyramid cells were but rarely normal, both lateral columns have been found degenerated. In one of the three cases lately described by Kingdon and Russell there was an extensive apparent sclerosis of the pyramidal tracts, and in the pons, the medulla, and the spinal cord. They suggest that possibly many of the pyramidal fibres may never been myelinated.† Moreover the anomalies of the brain and the cord are not contiguous; indeed just as little so, as for instance, in a disseminated sclerosis in which pons and the upper part of the cord may be quite normal, while there are similar and cotemporaneous changes in the cerebrum above and the cord below. In H. Higier's case (quoted from *Deutsche Z. f. Nervenheilk*, x., 1897), which occurred in a family in which two infants had previously died from probably the same condition, there was thickening of the retina in the area of the macula, excavation of the papillæ and atrophy of the optic nerve fibres. There was no vascular disease or inflammatory process; but atrophy of the cortical pyramid cells, descending degeneration of the whole pyramidal tract, and degeneration of the motor root of the trifacial nerve and of the pedunculi cerebelli.

The chiasma was found normal. The blood-vessels were also found normal, and there were no evidences, we are told, of anything like an "inflammation," at least, such as could be traced to the blood-vessels.

Now, what is the morbid process underlying the progressive, intellectual and physical change and decline? A mere arrest of development in early embryonal life, which has not been

* The internal ear does not suffer, or seldom suffers, in this disease. It is developed from the outer ectoderm, while both retina and optic nerve are, like the brain, from the medullary tube of the ectoderm.

† In all of their cases the cerebellum presented no evidence of degeneration or other change in the cells of Purkinje or those of the corpus dentatum.

proven, but presumed to exist by Dr. Sachs, cannot cause a *progressive* change such as is illustrated by the increase of idiocy and paralysis, and of the visible gradual alterations of the retina in a child that at first appeared normal.

The optic tissue consists primarily of radiated spindle-shaped cells which resemble the spindle-shaped cells primarily found in the early stages of the brain.

The suggestion is justified that the normal and the abnormal development of these spindle-shaped cells may go on *pari passu*, both in the embryonal eye and in the embryonal brain. Embryologists and histologists will perhaps elucidate the connection existing between the degenerative processes—which possibly is of an inflammatory nature originally—in cases like ours, and the accompanying ocular cerebral and spinal defects. To speak indiscriminately of a degenerative process pure and simple, without inflammation, either acute or chronic, is a questionable procedure as long as we are not certain or unanimous as to the essential requirements or character of "inflammation." Moreover it should be remembered, that in several instances, sclerotic processes, frequently the results of known inflammatory processes, are claimed for the cerebellum and other parts.

In connection with the definition of "inflammation," I suggest the following extracts from two sources: We read in Delafield and Prudden, a hand-book of pathological anatomy and histology, 5th Ed., 1896, p. 107: "The phenomena which are embraced under the name of inflammation are: degeneration and death of tissue; changes in the circulation of the blood; escape of the elements of the blood from the vessels; formation of new cells and new tissue. *These morbid changes either occur separately or are combined* in various ways. The growth of the body of pathogenic micro-organisms and the formation by them of toxic substances is a frequent inciting cause of inflammation;" and in *E. Ziegler Lehrb d. Allg. Pathol u. d. Pathol. Anatomie*, 9th Ed., 1898, I., p. 322, as follows (translated): "Inflammation may be caused by mechanical, thermic, electric or chemical influences, or by parasites. All these noxæ have this in common, that they produce a *local degeneration of tissue*, which *—when it is extensive or intense—is combined* with disorders of circulation and of vascular secretion." (Italics mine—A. J.)

The latter, therefore, should not be expected in every form or case of "inflammation," and to speak of degeneration in contra-

distinction to inflammation is rather a hazardous procedure in many instances.

The causes of an inflammation are not specific at all. Any noxa or injury may produce it, provided it be sufficiently intense to cause both degeneration of tissue and certain disorders of circulation, without producing complete interruption of circulation and necrosis of the tissues. The rapid physiological evolution of the spindle-shaped cells composing at that early period, both the optic tissue and the cerebrum furnishes the possibility of pathological alterations. Developmental over-activity in the embryo and fœtus may be looked upon from the same point of view as post-natal functional over-activity. The pathological anatomy of the newly-born heart or of the rhachitic bone or of the over-exerted muscle of young or old prove the close proximity of physiological and pathological conditions. That is why I cannot divest my mind from supposing that the degeneration which has been described as common to the few autopsies of such cases as ours was originally of an inflammatory character. Though it should be remembered, that there may be extensive cell degenerations without *marked* disorders of circulation, resulting for instance from the influence of toxins.

The thickening of arachnoid and pia and the hardness of the cerebral substances noted in one of the autopsies hitherto made, appears to point in that direction. It appears not unreasonable to suppose that the same inflammatory (proliferative, hyperplastic and by and by perhaps finally cicatrizing) process takes place in the macula lutea, or what is to *become* macula lutea.* Its late development would explain why (while undoubtedly the anatomical conditions of idiocy may be nearly developed at birth, the alterations of the macula lutea are discovered late;

* Macula lutea is absent from the embryonal retina; even from that of the newly-born. According to Huschke and other older authors it is a remnant of the ocular fissure; in the opinion of many the fovea centralis represents the upper remnant of the retinal fissure. Würzburg states that the formation of the macula lutea is preceded by a duplicature—a fold of the retina; still, these duplicatures are met with in several parts of the retina. At the very spot where the fibres of the optic nerves enter in later stages, the interior of the eye, there is, according to Bergmeister, a layer of cylindrical cells during embryonal life. Here the edges of the coloboma are turned up and rarefied, while in the rest of the eye the margins join one another. In this way the physiological excavation is formed.

S. L. Schenck, Lehrbuch der Embryologie des Menschen and der Wirbelthiere, Wien, 1896, 2d Ed., p. 187.

why they gradually get more pronounced and more destructive; and why they need not always—as instanced in Koller's case—appear at a regulation time.

The child whose case was discussed before the annual meeting of the American Neurological Association of 1898, by Dr. F. Peterson, was born of a German mother twenty-eight years old, the father being a Russian, twenty-nine years old, both of the Semitic race. Their first child is seven years old and normal, the second is an idiot of five and one-half years of age that became blind at six months, the third is a normal child of four years, the fourth was observed to be blind when four weeks old and died idiotic at ten months of age, the fifth died at the Randall's Island institution when seven months and twenty days old with the symptoms of amaurotic idiocy. It was said to have played and laughed up to the third or fourth month. There were measles at five months, followed by diarrhœa; the media of the eyes were clear, the pupils equal and somewhat dilated (normal?). There was no tremor, but gradually a rotatory and up and down ocular spasm was noticed, the neck and knees became rigid, the surface exhibited some purpuric spots, and the child died. The autopsy was made by Drs. McAlpin and Ewing. The lungs showed broncho-pneumonia; the kidneys were congested; the other viscera were all normal; the liver showed some fatty infiltration; the brain weighed 22 ounces; its surface was œdematous. The condition of the two halves was identical. The cortex was deficient in cells, all of them were of minute size and moderately deficient in chromatic substance. The same condition was noticed in the motor areas. In the cervical cord the cells of the anterior horns were normal, below this normal region they were less in number and shrunken; the cells of the olives normal and abundant, of the corpora quadrigemina and geniculata less and small, those of the sympathetic ganglia of the aorta of the spinal tract, and of the optic nerve and chiasma, normal; and the connective tissue rather deficient in the brain, but not so in the spinal cord. While in the normal infant brain the cells are arranged in distinct vertebral and longitudinal columns, almost all the vertebral columns were missing, while the longitudinal rows were indistinct. Dr. James Ewing characterized the main features of

the specimen as small size and small number of cells, and increased number of blood-vessels.

In the discussion following the report of this case Dr. Ward O. Holden who had examined the eyes, stated that vacuolation was found in the ganglion cells of the eyes, but the nuclei were not granular and the nucleoli were distinct while Nissl's granules were present in the cell bodies. There were no thorough changes. Moreover he stated that the results of the autopsy might be incorrect because it had been made forty hours after death. As an instance of the import of *post-mortem* changes he related that bacteria coli were found in the blood-vsssels, and from his remarks it seemed as if the diagnosis of amaurotic family idiocy might be doubted.

In the same meeting Dr. Wm. Hirsch detailed a case, the history of which was accompanied with extensive and elaborate demonstrations. There is no report which excels it in completeness and accuracy.* L. P. was seen first in July, 1896, when ten months old. It developed fairly until it was six months old. The mother, who lost two children when they were eighteen and twenty months old, respectively, reported that the child then became weaker and the muscles flabby. At that time there was some perception of light; reflexes were good, viscera normal, and the ophthalmoscopic appearance like that described above. It died July 17, 1897, and the autopsy was made four hours after death. The dura was adhering, the pia normal; there was no fluid and no œdema; no macroscopic anomaly, except a prolongation of the second temporal fissure.

Specimens were hardened in formalin 10 per cent.; one eye in formalin, one in Müller's fluid, and sections made in paraffine. Methylene, eosin, or hæmatoxylon were employed for staining purposes. The pyramidal tracts appeared degenerated as others observed them. In the cells of the anterior and posterior columns the nuclei were well defined, also the nucleoli; both of them were in many instances found near the edges of the cells. The cells were large, that is why they appeared too numerous. The motor cells were of double size, some apparently without nuclei, an impression mostly due to obliquity of section. Very few axis

* Dr. Hirsch gave me his manuscript to read, and demonstrated to me in his laboratory many of his charts and microscopical specimens, and kindly gave me some characteristic ones for presentation to the American Pediatric Society. His own complete report will undoubtedly appear soon.

cylinders and dendrites. Pericellular spaces small or absent. The nuclei surrounded by a dark zone. Nissl bodies disappear entirely in a granular mass. The light area contains a fine network; few normal chromatic bodies; medulla oblongata is found in the same condition, the changes in nuclei and cells are as above; in the olivary bodies the nuclei are markedly round; in the reticulated they are oval-shaped and pushed to the extreme end of the cells. In the cells of the trifacial nerve the nucleoli are hardly recognized. In the pericellular lymph spaces there are masses of detritus. Subcortical ganglia, thalamus and cortex are in the same condition. The pyramidal cells are changed and swollen, with displaced nuclei; also Purkinje's cells of the cerebellum.

The points Dr. Hirsch mainly emphasizes in connection with our subject are these: All the nerve cells, as far as examined, are changed in a peculiar way. There is chromatolysis and other degeneration. The cell bodies are large. The nuclei are displaced sideways. Neuroglia and blood-vessels are normal. Differences in the accounts of previous observers are explainable by insufficient methods of hardening or staining; Müller's fluid, for instance, shows the enlargement of the body of the cell but not its finer structure. The observed changes are pretty universal; there is neither an arrest of development nor a localization in the cortex, but as Kingdon and Russell assume, an acquired degeneration.

Where is its cause? As the infant is in good condition at first and the macula normal, the cells should be considered normal. No part of the embryonal history explains the future illness, which must be acquired. As the blood-vessels are found normal the process is not inflammatory(?). No systemic disease explains all the cell changes; there is no atrophy. That is why Dr. Hirsch believes that the only possible explanation is furnished by the presence of a toxic condition, which would correspond with experimental poisoning, the effects of which on the nerve cells, and on general nutrition, are different from all other disorders. What is the nature of the toxic substance? Perhaps the examination of the mother's and the infant's blood, and that of the mother's milk, will lead to the solution of the problem. At all events, Dr. Hirsch feels like weaning such infants, or refusing the mother's breast to any baby whose family history prevents cases of the same condition.

In connection with Dr. Hirsch's paper the characteristic appearance of the macula was made the subject of discussion by Dr. Ward O. Holden. He alluded to Treacher Collins, who explained the red spots by the thinness of the retina in the fovea centralis, while round about there was, in his opinion (which, however, he doubted himself), an intense œdema. This alleged œdema is, however, found in the healthy eyes of dead persons, and may result from the following of the retina round the macula in that condition. The real cause of the red spot surrounded by white discoloration is, according to Dr. Holden, as follows: In the periphery of the retina where the cells are scattered, they are large. In the macular region they are several (6–7) layers deep and mostly small. In the peculiar degenarative process of amaurotic family idiocy these cells are of increased (double) size, and their contents dense and turbid. Hence the white discoloration. The fovea centralis has no layer of ganglion cells—hence the choroid shows through.

The atrophy of the optic nerve is always observed long after the changes in the macula lutea. It develops very gradually. According to Koller, the behavior of the children with regard to their vision was not normal at a time when no ophthalmoscopic changes were visible, so that the conclusion is permissible that vision had been impaired by cerebral degeneration. (*New York Medical Record*, July 9, 1898.)