DIFFUSE WHITE MATTER GLIOSIS IN MENTAL DEFECTIVES.*

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THIS paper is a preliminary report of some investigations we are now making into the pathology of mental deficiency, mainly from the histological point of view. We have so far examined 22 cases, comprising 7 low-grade defectives showing gross neurological lesions, chiefly of extrapyramidal character, 6 microcephalics with spastic diplegia and severe mental defect, 2 able-bodied microcephalics without gross neurological signs, 1 simple able-bodied idiot and 6 mongols. In this short paper it is impossible to give even the slightest indication of the wealth of pathological material found in such a variety of widely differing conditions. A full description of our findings, together with a more detailed discussion, must be left to further papers dealing with individual groups of cases. The purpose of making a short note at this stage is to draw attention to one particular finding which struck us by its surprising constancy, i.e., a proliferation of the fibrous glia, particularly pronounced within the cerebral and often also the cerebellar white matter. In many of the cases the cortical changes were slight compared with the intense lesions of the white matter. In none of them was demyelinization a well-marked feature, nor did its severity approach that of the glial proliferation; in many it was negligible, and there were none of the fatty breakdown products, characteristic of the demyelinizing disease of the white matter called after Schilder. The gliosis was either diffused or patchy, and was often markedly perivascular; even stripe-like scars, as described by Hallervorden (10), were to be seen, although, contrary to this author's observation, there was, as a rule, no corresponding myelin defect.

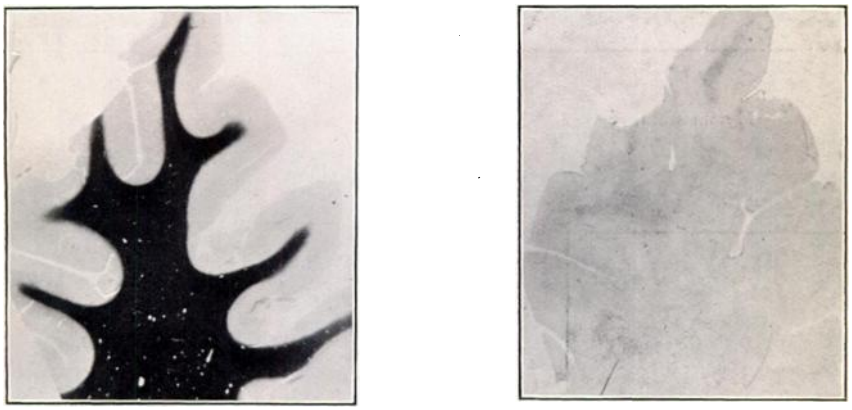
The gliosis of the white matter was observed in cases of *état dysmyélinisé* of the globus pallidus, *état marbré* of the striate body and in related progressive conditions, commencing at birth or in infancy. It was found in all but one of our microcephalics, whether they were associated with gross developmental disfiguration of the convolutional pattern or not. Its presence in "microcephalia vera" (8, 1, 12, 4, 14, 9), that is to say, in cases of pachygyria, microgyria and heterotopia not complicated by gross destructive lesions, such as

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porencephaly or hydrocephaly, was quite unexpected. The maldeveloped cortex and the heterotopic areas within the white matter were always free from gliotic proliferation except for occasional sub-pial gliosis. The one exception mentioned above was a familial microcephalic. In this brain the most striking features were circumscribed heterotopias in the region between the insula and the putamen, and it must be more than a coincidence that H. Jacob (11) has described an exactly similar state of globular heterotopia without gliosis in familial microcephalics also. It may well be that cases of this type belong to a special group.

Of particular interest are naturally the findings in the brains of three able-bodied low-grade defectives and in all six mongols available for examination.



a Weil's myelin stain. *b* Holzer's glia stain.

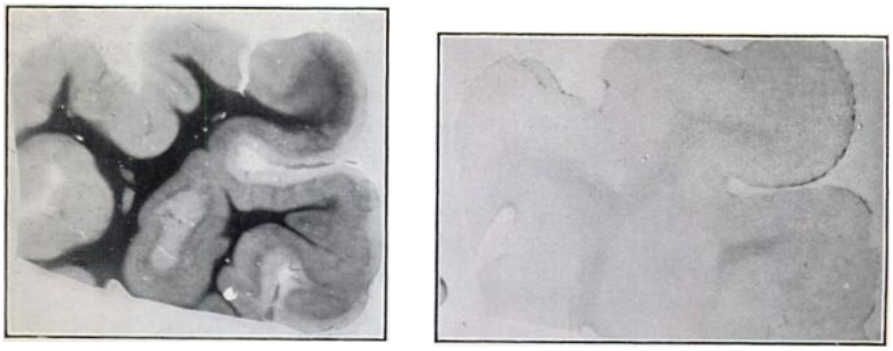
FIG. 1.—Able-bodied defective.

One of the able-bodied microcephalics had, apart from the diffuse lesion in the white matter, slight scarring in the striate body and the thalamus. Another showed a mild demyelinization of the type seen in the Pelizæus-Merzbacher disease. In two of the mongols, incidentally the youngest in our material, who died at the age of 18 months and 3 years, the lesions within the white matter were very diffuse, whereas in the others they were of a patchy and perivascular type. Gliosis of longer standing was found combined with that of more recent appearance, somewhat independently of the age of the patients, which varied from 18 months to 20 years at the time of death. As a rule, subependymal regions were particularly affected.

A few photographs are included in order to show the characteristic localization of the gliosis. Fig. 1 shows a diffuse (though occasionally patchy) gliosis without demyelinization (Fig. 1*b*) in the white matter of one of the able-bodied microcephalics. Fig. 2 shows a similar condition in the white

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matter of a microgyric microcephalic. The clear spaces in the myelin picture (Fig. 2*b*) indicate heterotopic areas which are spared by the gliosis. The



a Myelin stain. *b* Glia stain.

FIG. 2.—Microgyria.



a Myelin stain. *b* Glia stain.

FIG. 3.—Mongol.

same characteristic white matter gliosis without a marked degree of demyelinization is shown in Fig. 3, which is taken from one of the younger mongols. The sclerosis of the vulnerable Sommer sector in the cornu ammonis should be especially noted. It will be seen from the photograph that the full extent of

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the lesions is brought out only by fibro-glial staining (Holzer), myelin and cell pictures giving no real indication of what we were to find. This perhaps explains why the glial scarring in these conditions has so far been largely overlooked, routine brain examinations and architectonic studies being often confined to cell and myelin stains.

Discussion.

An adequate attempt at interpreting the findings would require a far more detailed presentation of the clinical and pathological data than has been possible in this paper. We shall confine ourselves, therefore, to a brief discussion of the main points.

Gliosis, with little or no demyelinization and other breakdown changes, has been reported already by Freeman (7) in the brain-stem of diplegic microcephalics, and by Bodechtel and Guttmann (3) in cases of diffuse sclerosis. More recently Scherer (13) has described the same type of lesion in the cerebellar white matter as an important feature of olivo-ponto-cerebellar degeneration, and Davison (6) has found gliosis without demyelinization in the occipital lobes in Huntington's chorea. In all our cases the gliosis showed no difference from that seen in conditions of adult life, and there were none of the immature or blastomatous glia-cells characteristic of developmental errors, such as are to be seen in tuberous sclerosis, von Recklinghausen's disease, etc. The idea that non-developed brain-tissue is simply replaced by glia has little factual basis, and only serves to obscure the true pathogenic interpretation of the findings. As to the microgyric brains, the appearance of the white matter gliosis in regions where cortical disturbances were negligible, e.g., in the cerebellum, suggests that the gliosis was not secondary to the malformation of the cortex. It is interesting to note how often pathological processes accompany developmental lesions (in one case only of our series were developmental changes found alone, and this was significantly a familial microcephalic), and undoubtedly in some cases they may be their cause. More often than is realized developmental arrest is only the indicator of the time of the damage, and not the expression of an intrinsic, abiotrophic or faulty tendency of the tissue. This is a point of particular importance, because the belief that mental deficiency in general is due to an innate developmental inability, which might be diffuse or localized, is still widely popular in this country.

The pathogenesis of the gliosis is at present obscure. There is, however, in many of our cases some evidence suggesting that a vascular factor or some other type of defective tissue oxygenation might be the immediate cause of the change. The lesions peculiar to *état marbré* and *état dysmyélinisé* are considered by some to be due to vascular disturbances. In one of the mongols the Sommer sector of the cornu ammonis showed a well-marked sclerosis, and, in addition, there were, in the mongols and in other cases, perivascular

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changes as well as the diffuse lesions. The findings of Schwartz (15, 16) in birth-trauma and of Bodechtel (2) in congenital heart disease point in the same direction. It should be borne in mind, however, that defective tissue oxygenation is often merely a final common pathway of ætiologically different disease processes.

No generalizations can be made as to the glial changes acting as a substrate of the mental defect. This interpretation could be made only after evaluating all clinical and pathological data in the individual cases. Moreover, our material of able-bodied defectives, all three of them low grade, is too small to allow of generalization. The findings in these cases, however, give a forcible warning against indiscriminate use of such brains for comparative purposes, e.g., measurements of the cortex, which are liable to grave error unless a systematic investigation of the whole brain is made.

The interpretation of the pathological changes is particularly difficult in the mongols, who, apart from their mental defect, are distinguished by a feeble bodily constitution, frequently associated with disturbances of the vascular system and a susceptibility to infections of all kinds. The changes described, however, are unlikely to be due to the terminal disease, which was very short in our cases, death occurring even suddenly in some of them. Moreover, congenital heart disease was lacking in four of the six cases, including the case illustrated in Fig. 3. The constancy of the lesions is striking; they throw some new light on occasional observations reported by previous writers (see Davidoff's (5) review). Further evidence is required before the full significance of the changes can be assessed.

This necessary restraint in the interpretation of the findings should not obscure the fact that the extremely high incidence of lesions within the white matter adds a new feature to the pathology of mental deficiency. Bodechtel (2) has already expressed the view that it is the white matter which is particularly susceptible to oxygen deprivation in the developing brain, in contrast to the adult brain, in which the cortex is more vulnerable. Our own investigations confirm this on an unexpectedly large scale. In emphasizing the importance of the white matter, we do not wish to disparage that of the cortex, the integrity of which is, of course, essential to the development of normal intelligence. Traditional ideas, however, derived from genetic considerations, do make it necessary to stress the obvious conclusion that any research into the pathogenesis of mental defect requires impartial examination of all parts of the brain.

To Mrs. A. Meyer and Mr. Wright we owe thanks for the histological preparations, while for case-material and other help we are indebted to several colleagues, to whom individual acknowledgment will be made in subsequent papers.

References.—(1) Bielschowsky, M., *Journ. Psychol. u. Neurol.*, 1923, xxx, p. 1.—(2) Bodechtel G., *Zeitschr. f. d. ges. Neur. u. Psychiat.*, 1932, cxl, p. 657.—(3) *Idem* and Guttmann, E., *ibid.*, 1932,

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cxxxviii, p. 544.—(4) Brunschweiler, H., *Schweiz. Arch. Neur. u. Psychiat.*, 1927*a*, xxi, p. 246 ; 1927*b*, xxii, p. 73 ; 1928, xxii, p. 269.—(5) Davidoff, L. M., *Arch. Neur. u. Psychiat.*, 1928, xx, p. 1229.—(6) Davison, C., *Amer. Journ. Psychiat.*, 1935, xcii, p. 361.—(7) Freeman, W., *Brain*, 1927, l, p. 188.—(8) Giacomini (quoted by Brunschweiler (4)).—(9) Greenfield, J. G., and Wolfsohn, J. M., *Arch. Neur. u. Psychiat.*, 1935, xxxiii, p. 1296.—(10) Hallervorden, J., *Zentralbl. f. ges. Neur. u. Psychiat.*, 1932, lxiv, p. 730.—(11) Jacob, H., *Zeitschr. f. d. ges. Neur. u. Psychiat.*, 1936, clvi, p. 633.—(12) von Monakow, C., *Schweiz. Arch. Neur. u. Psychiat.*, 1926, xviii, p. 3.—(13) Scherer, H. J., *Zeitschr. f. d. ges. Neur. u. Psychiat.*, 1933, cxlv, p. 335.—(14) Schob, F., *Bumke's Handbuch der Geisteskr.*, 1930, xi, p. 779.—(15) Schwartz, P., *Zeitschr. f. d. ges. Neur. u. Psychiat.*, 1924, xc, p. 263.—(16) *Idem*, *Ergebn. inn. Med. Kinderheilk.*, 1927, xxxi, p. 165.

Discussion.

Dr. GUTTMANN expressed his appreciation of Prof. Meyer's interesting and impressive anatomical findings which he had just presented, especially his remarks on the able-bodied imbeciles whose brains he had examined. What Prof. Meyer had said naturally drew attention to the clinical side, and led one to ask what symptoms could one expect in patients with brains like those described and depicted ? There might be several reasons why so little was known about the symptoms in these so-called able-bodied imbeciles ; it might be that the symptoms were of a different kind from anything hitherto discovered ; or it might be they were not found because they were not looked for. Such findings as sclerosis of the grey matter of the occipital lobe pointed to the importance of investigating the visual functions. The main point seemed to be that there might be symptoms which were known, but their correlation with anatomical findings was not known. During the last decade a good deal had been learned about the anatomical basis of psychological symptoms. He reminded members of the disturbances of initiative when lesions were present in the frontal area of the brain, or disturbances of expression and of personality after encephalitis with its well-known anatomical lesions.

However, it was only to a small section of such symptoms and their possible anatomical relation that he wished to direct attention. Prof. Meyer had mentioned that perhaps the more exact analysis of disturbances which were known in imbeciles, such as their clumsiness, might lead to the possibility of correlating those symptoms with the anatomical findings.

He intended to show a few pictures ; he did not claim to show anything new. He asked members to look at those clinical pictures from a neurological angle, which need not exclude the psychological aspect of these conditions, but would simply give another approach to these problems. He was indebted to Dr. Lindsay, and especially to Dr. Earl, who gave him and his colleagues access to some of the material which would be seen in the film. This was only a sample of their collection showing things which everybody approached from the psychological side, but which were now being approached neurologically. The athetotic movements and facial expressions were now regarded as neurological symptoms and not as mere grimaces. It was difficult to determine these movements in stereotyped idiots. There were pictures of feeblemindedness which might point to sensory disturbance as being at the bottom of the whole clinical picture. Of that little was yet known ; they were only collecting information which possibly might be interpreted in the light of these anatomical findings.

[Dr. Guttmann here showed a film illustrating various disorders of motility.]

In the first part of the film there was shown a boy whose emotional expression started locally in the face, and then spread so that the whole body became violently contorted. Another boy shown had an athetotic lesion and a peculiar facial expression. Next there was a young woman who suffered from a disturbance of the first impulses in the act of walking. There was not yet a method of analysing them from the neurological standpoint. He directed attention to the patient's high stepping. There was also seen in the film a patient with motor infantilism ;

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it showed a method of grasping things without using the thumb; and there were movements similar to those seen in encephalitis.

Dr. W. R. ASHBY said that one point in Prof. Meyer's paper which had interested him very much was the widespread character of the lesions. That accorded with a view he had held for a long time, in contrast to statements in many of the earlier books. People who wrote on the subject years ago seemed to have the idea that intelligence was localized to some very small area of the brain. At first it was thought to be in the cortex, and later it was even more narrowly allocated to the frontal lobes, then to the prefrontal area. Many anatomists hoped, at that time, that they would ultimately find that small spot. His own view was that intelligence would be found to be more a function of the whole brain. The matter might be compared with the case of the athlete. No one expected the athlete to be the man with the longest possible legs, or the biggest heart; it was recognized that the athlete, to be first-class and efficient, must be a well-proportioned person. If his legs were made twice as long, then, instead of doubling his speed on the track, it would upset his performance. He asked whether Prof. Meyer considered that intelligence could be a function of the whole brain, and not one which was restricted to a particular area of it.

Dr. F. A. PICKWORTH said: The changes in the white matter of the cases which Prof. Meyer has described are often regarded as a primary gliosis, and I am glad to hear that Prof. Meyer believes that at least some are consequent upon an anoxæmia. Spasm or occlusion of blood-vessels is known to kill the vulnerable nerve-cells, allowing the more resistant glia-cells to survive, and these later increase with restoration of the blood-supply and the stimulus of the contiguous products of degeneration.

Taking mental deficiency in general I believe that occlusion of capillary brain vessels is a primary factor of real ætiological significance, and which is not necessarily restricted to any stage of development. In the developing embryo the period of competence of certain cells is strictly limited, and J. Needham showed that once this period has been passed without cell differentiation, no amount of auxins or sterols can ever make them develop normally afterwards. It is equally obvious that occlusion of nutrient vessels occurring at any period of intra-uterine life and in infancy hinders local growth, and results in a disproportionate development of such areas in respect to the rest of the brain. Environmental stresses necessitate that certain reflexes and mental activities shall be met by other functional systems to the detriment of the organism as a whole, and thus forming the essential basis of mental defect.

Of the causes of the vascular defects, birth trauma is probably the most important, although signs or symptoms of such injury may not be recognizable until long after birth. In my book on *Chronic Nasal Sinusitis and its Relation to Mental Disorder* I illustrate (fig. 26, p. 58) bacterial organisms as a cause of cerebral vascular defect. In this connection the importance of a bacteriæmia in the mother during the first few weeks of pregnancy is obvious, as recent researches have proved that a bacteriæmia from dental sepsis, for example, is of quite common occurrence. In the millions of chances provided by such bacteriæmia, an involvement of the placenta and passage of bacteria into the fœtal circulation to cause such changes in the cerebral capillaries is by no means a negligible consideration. A practitioner with much experience with mental defectives recently told me that he was very much impressed with the frequency he had obtained a history of a chronic septic condition in the mothers of defective children during the first few weeks of pregnancy.

An association of body deformities and metabolic or endocrine disturbances with mental deficiency is found in the pathetic creatures of institution nurseries, and such associations suggest vascular injury of the diencephalon. The vascular defects of spasm, thrombosis and hæmorrhage occurring at various stages of

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development and in various localities of the brain to my mind can account for many clinical syndromes at present considered hereditary diseases.

The mechanisms I have demonstrated in the adult, of the relation between nasal sinus infection and pituitary hypothalamic dysfunction, are of equal importance in infancy, since chronic nasal infection may be established within a few weeks of birth. The specimen now shown is the sphenoid of a child only three months old, but which contains pus in the left spheno-ethmoidal recess as the most striking post-mortem finding. As a student I saw a case of mental deficiency which developed normally until nine months old, when a discharge from the ear was noted (the ear condition being probably part of a general nasal sinus infection), and only many months after this infection had subsided did the absence of further mental development become apparent. The clinico-pathological picture is that of a subclinical basal meningitis with thromboses of many of the cerebral capillaries to such an extent that further local cerebral development was inhibited until too late. Such cases, I believe, are commoner than generally supposed, and a recognition of this type of ætiological pathology will bring many cases of incipient mental defect within the realm of economic and preventive medicine.

Dr. JONES (Caterham) said he would like to tell the meeting about a case which he examined after death last month, and which supported Prof. Meyer's contention. He was an able-bodied imbecile, and the white matter of the brain showed dense gliosis in the occipital region, in the cerebellum and in the brain-stem. The characteristic was that the corresponding myelin picture showed either normal demyelinization or only a small fraction of the normal. The gliosis was most marked in the occipital region, and in the islands of the cerebellum and the brain-stem. There was a rarefaction in the centre of the white matter. He showed a slide demonstrating this case, and another slide showing corresponding gliosis in the region of the fibres, without demyelinization.

Dr. W. F. MENZIES said he wished, first, to correct a false impression. Dr. Ashby had just said that intellectual power had been supposed to be resident in one small part of the cortex. He, the speaker, had never heard a psychiatrist put forward such a view. For fifty years it had been known that intelligence was a matter of association of every part of the brain.

He wished to mention two cases of choreo-athetosis which were in the imbecile block at Cheddleton, in respect of which he would like some information. Why had those cases such extreme hypogonadism? The brain of one was, when he left Cheddleton, in process of being hardened. That boy could not speak at all, and when he tried to he made violent contortions, and these were seen whenever he tried to express any emotion, the motions affecting the whole body. The bowel and bladder reflexes, however, were not interfered with at all, and apparently his intelligence was normal when judged by his replies to questions; he enjoyed the cinema and liked to watch dancing. He had extreme hypogonadism; up to eighteen years of age he had no hair on the pubes, and the penis and testicles were very small. Then suddenly, in the course of the next year, an immense growth of the generative organs took place. Shortly afterwards he caught influenza, then pneumonia, and died.

The other case was that of a girl, now about twenty years of age, and very intelligent, in fact, a nice child. She used to like the nurse to read stories to her, and she especially enjoyed fairy tales, which she seemed to understand. But she was unable to speak a word. She was now learning to say a very little, and responded to questions with the ejaculation "Ya" if she approved, shaking her head in token of negation. She, also, had extreme hypogonadism; she had never menstruated, had no pubic or axillary hair, and the mammæ were not developed. Her glands were almost intangible. He asked whether those who had investigated cases of choreo-athetosis had gone into the question of the gonads.

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Dr. B. H. SHAW remarked that the cases which had been described and depicted were those with very grave defects. He had noticed pathologically that in cases of mild mental deficiency there was a definite lessening of the granular nuclei in the cerebellum. Normally the diameter was a very constant figure—4·5μ—but in mental enfeeblement the diameter was much less—as much as 25% less, for in many of these defectives it was no more than 3·7. That he regarded as of some moment.

With regard to the question of gliosis, he had had two cases among his epileptics with peculiar movements. Both cases, when they had a fit, revolved in the same direction, i.e., right to left, quickly, just before the actual fit, and continued afterwards. In both cases he found that the lesion was a gliosis of the periphery of the cerebellar cortex on the right side. The fits dated from an attack of acute rheumatism.

Dr. MEYER, in reply, thanked the members very much for their kind reception of this crude attempt to tackle again, after so many failures, the big problem of mental deficiency. He was particularly indebted to Drs. Earl and Guttmann, as they had rendered him most valuable services, especially in putting his description into a more clinical form. It was that which he had in mind when he asked for a more refined neurological approach in regard to the so-called able-bodied defectives.

In reply to Dr. Ashby, he would consider that it was always the whole brain which worked in normal and in pathological conditions; but there might be a localizable defect, which might differ in site with different conditions. It was possible that future analyses of mental defectives would make it possible to differentiate between the one whose visual perceptive side was good, and the one who had a number of defects. Earl had pointed out that it was the emotional sphere which had hindered normal development, and it was that which might even help, under certain circumstances, to overcome the defect.

What Dr. Ashby did not mention was another interesting point brought about by his own research on the biochemical side. It had been pointed out that some biochemical abnormality might be due to lack of neurons, or to an overgrowth of neuroglia, and he would like an opinion as to whether that overgrowth of neuroglia in able-bodied people did not fit in with some of Dr. Ashby's conceptions.

He agreed with what Dr. Pickworth said. He was sorry he had been misunderstood. Nothing could be known about the nature of the process unless one knew the earlier stages; and from what he had seen he stressed the possibility of anoxæmia being a possible cause. That would fit in with Dr. Pickworth's suggestions and findings.

He thanked Dr. Jones for his remarks, because that gentleman brought the first confirmation of the gliosis, which now enlarged the very limited material, and consolidated a little the position which had been taken up.

With regard to the remarks of Dr. Menzies on hypogonadism, in his own cases of choreo-athetosis there were no lesions of the testicles found, but choreo-athetosis was a symptom only. The choreo-athetotic cases he had shown were probably due to birth trauma and to anoxæmia. He had seen many cases of choreo-athetosis which would not show the changes he had described. He had seen a case of amaurotic idiocy developing from the choreo-athetotic stage and passing into a demented stage. Without examination of the brains of the cases of which Dr. Menzies spoke it was impossible to form a definite opinion on hypogonadism. It was, however, very important to keep this in mind, he thought, and not to omit examination of the bodily organs, not only the testicles, but also the pituitary and other endocrine glands.

He was sorry not to have heard any suggestions in regard to the findings in mongols, which were so characteristic of anoxæmia. He had had many ideas about it; and one thing which was worth discussing was that heredity in mongolism was no longer recognized as a factor. According to Penrose and others it seemed to be the advanced age of the mother which was one of the most important factors; it might be responsible for an insufficient blood-supply reaching and nourishing

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the fœtus—the kind of thing which Dr. Pickworth probably had in mind. More facts, however, were needed to enable a sound opinion to be formed.

With regard to Dr. Shaw's remark concerning the granular layer in high-grade defectives, as he, the speaker, stated in his paper, he had not seen high-grade defectives, therefore he could not reply on that point. It was a very interesting one, and deserved full attention. If there was a deficient granular layer, one must consider whether there was or was not something behind that. He could well imagine that an affection of the white matter would also possibly lead to such a diminution of the granular layer. In his own severe case the granular layer was intact; it was only the white matter in the hilum of the dentate nucleus which was severely affected.

Again he thanked his hearers for their patient hearing.

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