HISTOLOGICAL CHANGES IN THE BRAIN IN MONGOLISM.

By A. MEYER, M.D.Bonn, and T. B. JONES, M.R.C.S., L.R.C.P., D.P.M.

(From the Central Pathological Laboratory of the London County Hospitals for Nervous and Mental Disorders.)

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THE investigations reported in this paper owe their origin to a systematic research on the fibrous glia in various groups of mental defectives. A preliminary note on this subject has already been published by A. Meyer and L. C. Cook (1937). For technical reasons the full report on these findings will be delayed. A special publication on the findings in mongols seemed to be desirable, not so much because they are thought to constitute the substrate of the mental defect in mongolism, but because they are so unusual that they deserve special mention. In addition, they throw some light on the findings and interpretations of previous workers.

So far the results of histological examinations of mongol brains have not been too satisfactory, as can be seen from recent reviews given by Davidoff (1928), Schob (1930), Kreyenberg (1936), Weigandt (1937), and others. There seems to be unanimity about the frequency of certain stigmata, such as subnormal average brain-weight, a certain simplicity of the convolutional pattern, and often a relative smallness of the brain-stem and cerebellum in proportion to the whole. Van der Scheer's (1927) claim that the hypothalamus is decreased in size in conjunction with a narrowness of the interpeduncular space has not been confirmed by subsequent workers (Davidoff (1928)), and the often described spherical shape of the brain has been entirely attributed to brachycephaly, the frequency of which has been questioned recently by Kreyenberg (1936). There is no unanimity with regard to slight changes in and decrease in number of ganglion-cells, particularly those of the third layer in the cortex, which are regarded by some as a developmental abnormality (Berry and Norman (1933–34), Norman (1938)), by others (Davidoff (1925)) as an expression of a late fœtal degenerative process which in some of Davidoff's cases led also to sub-ependymal softenings, increase of pseudo-calcium, etc. Other signs of a pathological process have been described by Villaverde (1931) in the cerebellum, by Orifice

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(1932), Babonneix and Lhermitte (1936), who regarded them as being of a syphilitic nature. This list, however, is by no means complete.

In our own investigations we have not made any attempt to contribute to these controversial points, a special study of the cortex by cyto-architectonic and myelo-architectonic methods not having been carried out. Our attention was arrested by the proliferation of the fibrous glia, and it is with these observations that the present paper is especially concerned.

Altogether 15 cases have been investigated. Of these 5 cases either showed no significant change, or the amount of fibrous glia found in sub-ependymal regions, olivary body, dentate nucleus and cerebellar white matter appeared to be normal.

The quantitative estimation of the glial proliferation is of course liable to subjective error, the more so since a systematic architectonic study of the normal fibrous glia and its variation with age is still lacking in spite of Weigert's (1890) original description and some later attempts by A. H. Schröder (1935), Opalski (1933–34) and others.

Studies in this direction are at present in progress in this laboratory.

CASE 1.—D. R—, female, aged 2¾. Admitted to the Fountain Hospital 13.iv.32.

Family history.—The patient was the first of two children. The mother was 35 and the father was 25 years old at the time of the birth of the child. The labour was premature and protracted, with forceps delivery. The other child is alive and well.

Personal history.—She was a typical low-grade mongolian imbecile. It was difficult to command her attention. She would not answer to her name, was wild and excitable and had screaming attacks if she was opposed in any way, or if her toys were removed. She was wet and dirty in her habits and had to be fed. She gave no response to tests.

On 18.ix.32 a lung infection was first recorded.

She died on 28.ix.32 from pneumonia.

Post-mortem examination showed consolidation of both lower lobes of the lung, dilatation of the right side of the heart and pericarditis with effusion. There was no congenital heart disease.

Macroscopic appearance of the brain.—The brain had previously been fixed in formalin and weighed 840 grm. The convolutional pattern was normal. The brain-stem was, however, rather too small compared with the rest of the brain, and the first temporal convolution was also slightly smaller than usual.

On coronal section the white matter, especially in the occipital, temporal and orbital frontal regions, presented a suspicious appearance, being greyish and in parts mottled. The cortex seemed to be of normal depth and pattern. In the occipital lobe there was a distinct appearance of *état criblé*. The cornu ammonis was very small on both sides.

Histological examination.—The macroscopic suspicion was confirmed by histological examination. The most striking picture was that of a very dense and diffuse gliosis, as shown in Holzer preparations. This was particularly marked in the white matter of the occipital (Fig. 1), temporal (Fig. 2) and frontal regions, but also in the pons, medulla and white matter of the cerebellum. It was also marked in intensity near the ventricular surfaces. In the medulla the dorsal regions of the olive were especially affected by the gliosis, but there was also much proliferation

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outside them. In the thalamus and hypothalamus the proliferation was confined to the sub-ependymal regions, exceeding the amount of fibrous glia seen here under normal circumstances. Apart from marked subpial gliosis, the cortex was little affected. Compared with the glia picture all other staining reactions were disappointing. The myelin picture showed some slight rarefaction, and in the occipital lobes (Fig. 1*a*) distinct small, roundish areas of demyelinization, some being perivascular and others without relation to vessels.

The brain-stem and cerebellum showed no demyelinization.

Products stainable by Scharlach R occurred only occasionally in scavenger cells in the perivascular sheaths.

In the small demyelinized areas of the occipital lobes no fatty products were seen, indicating that the changes were probably of older standing. The same impression was gained from Nissl-stained slides, in which apart from a general protoplasmic increase of macroglia no recent changes were seen.

The vessel walls were thickened and the perivascular sheaths enlarged, often containing pigment-carrying scavenger cells as well as some cells with fatty inclusions

In the cortex the ganglion-cell architecture was as a whole preserved and showed no gross abnormality.

No detailed cyto-architectonic investigation has been carried out. A detailed study of the hypothalamus is in progress and will be reported on later.

A striking feature was the presence of much fibrous gliosis near the supra-optic nucleus at the edge of the optic tract, which itself contained abundant glial fibres.

All the ventricular surfaces showed a definite increase of sub-ependymal glia.

Within the cornu ammonis a typical sector sclerosis was found. This was of old standing, as shown by the absence of recent breakdown products and the disappearance of ganglion-cells, which were replaced by dense fibrous gliosis (Fig. 2).

CASE 2.—B. F—, female, aged 7½. Admitted to Fountain Hospital 8.xi.33.

Family history.—The parents were unrelated, and were both 29 years old at birth of the child. The mother was stated to be " highly strung ". The patient was the last of three pregnancies. The first child is normal; the second pregnancy resulted in a miscarriage at three months.

Gestation and birth.—There was some hæmorrhage after a long 'bus ride at the third month of pregnancy. At six months there was severe vomiting, especially at night. The child was born at full term, unreduced right occipito-posterior with extended legs. The amount of amniotic fluid was normal. There was no premature rupture of membranes. The placenta was cyanotic in appearance. The birth weight was 6 lb., but soon dropped to 3 lb., and the baby was so flaccid that her head " flopped back to touch the middle of her back ". Her legs were deformed from birth and " appeared back to front ".

Physical condition.—A case of amyoplasia congenita associated with mongolism. She had congenital genu recurvatum, severe congenital equino-varus and cervical opisthotonos. Her musculature was very poor, ligaments very lax, and abnormal mobility occurred at all joints except at the knees and ankles, where deformity was present. Her general appearance, skin, hands, palate, ears, epicanthus, flabbiness, hypotonia, articulation, mannerisms and general personality were typical of mongolism.

Cardio-vascular system.—There was no obvious heart lesion. The peripheral circulation was poor, and she suffered from chilblains.

Central nervous system.—It was impossible to determine the knee-jerks and ankle-jerks owing to deformity. The tendon reflexes were sluggish, but equal. The plantar reflexes were flexor. The abdominal reflexes were present and equal. The Wassermann reaction and Meinicke reaction negative.

Mental state.—Her mental age approximated to two years. She could point to her nose, and obey simple commands, but was unable to execute two consecutive

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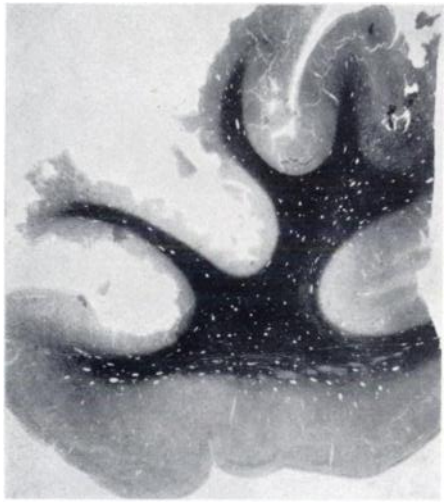


FIG. 1A.—Occipital lobe; Weil stain.



FIG. 1B.—Occipital lobe; Holzer stain.



FIG. 2.—Temporal lobe; Holzer stain.

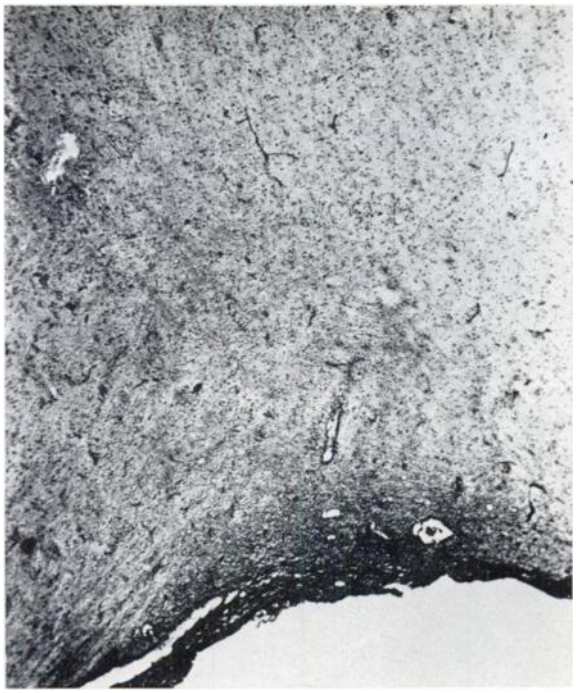


FIG. 3.—Frontal lobe; Holzer stain.

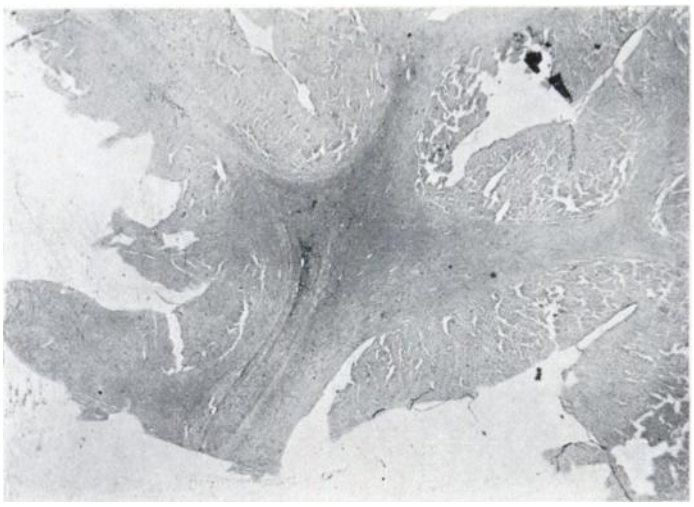


FIG. 4.—Occipital lobe; Holzer stain.

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FIG. 5.—Temporal lobe; Holzer stain.

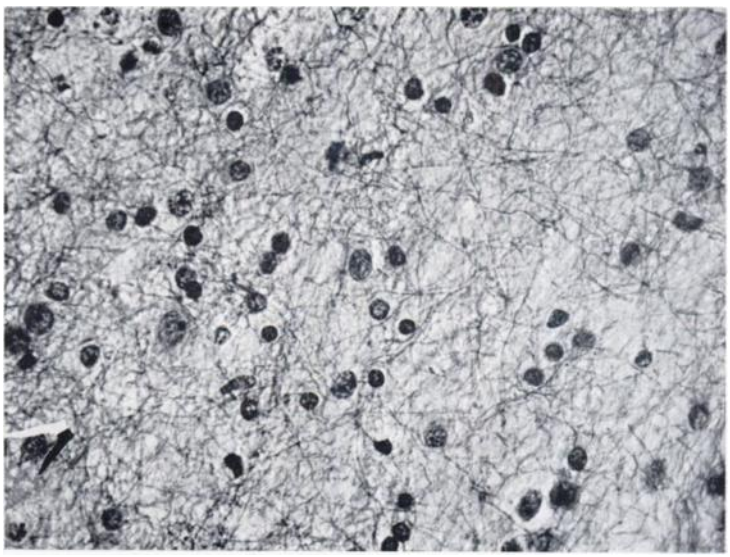


FIG. 6.—Temporal lobe; Holzer stain.

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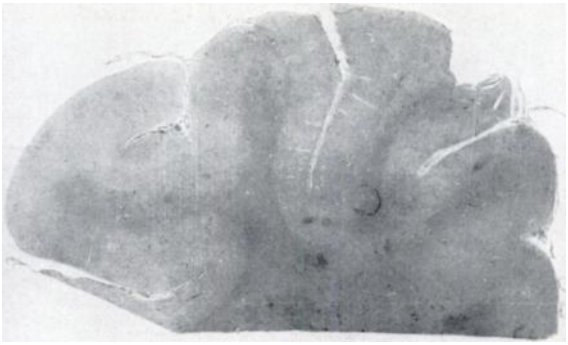


FIG. 7.- Temporal lobe Holzer stain.

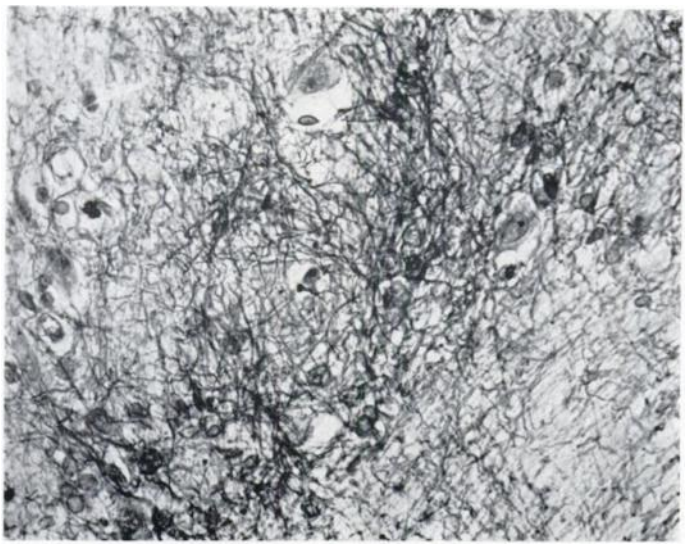


FIG. 8.—Temporal lobe ; Holzer stain.

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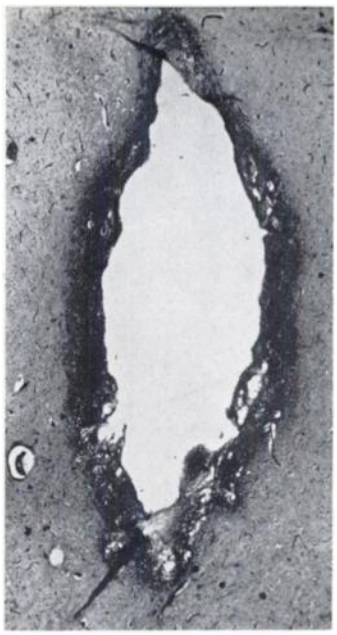


FIG. 9.—Aqueduct ; Holzer stain.

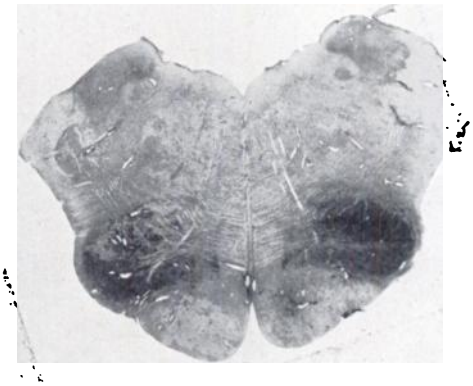


FIG. 10.—Medulla ; Holzer stain.

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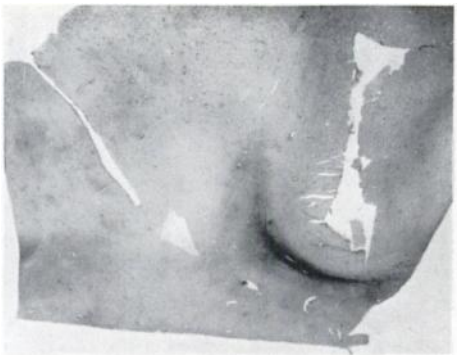


FIG. 11.—Occipital lobe ; Holzer stain.



FIG. 12.—Cerebellum ; Holzer stain.

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commands. She failed to give her name or sex. She was able to recognize a paper-wrapped sweet, and would undo it before putting it into her mouth. It was very difficult to engage her attention. She did not co-operate in any way. She was unable to use a spoon and made no effort to dress. Her habits were faulty. She was lively and mischievous, and aimlessly destructive to toys.

In January, 1934, she suffered from cellulitis of the right leg and thigh, in February from Vincent's angina, which cleared up rapidly after two arsenical injections, and in March from a feverish cold and cough. During June she became much more subdued and lacking in energy. No physical signs to account for this were present, but her appetite was poor and she was obviously unwell. She recovered, however, and was quite at her best until she contracted scarlet fever in September. On 7.i.35, she was put to bed with an ordinary afebrile cough and cold. No physical signs developed, but, as in June, she was very listless and "floppy". Three days later she died suddenly, shortly after sitting up in bed quite happily and comfortably.*

Post-mortem.—The subcutaneous fat was well marked, the muscles pale and exiguous. The heart weighed 184 mgrm. It was exceptionally large and heavy, with general muscular hypertrophy but no dilatation. The right side was full of dark clot. There were no congenital abnormalities. The liver was pale and greasy; weight 539 grm. Sections of the liver showed fatty degeneration and moderate venous engorgement. The thyroid approximated to a fœtal type. Acini small and colloid scanty. There was proliferation both of epithelial cells and of inter-acinous fibrous tissue.

The brain weighed 1,134 grm. A small tumour the size of a pea was found attached to the wall of the right lateral ventricle. Sections of this tumour revealed choroid plexus tissue. The brain was not as rounded in shape as is often found in mongols.

Histological examination.—There was a moderate fibrous gliosis in patches throughout the white matter, as shown in Holzer preparations. In some parts it was dense and poor in cells, particularly near the ventricles (Fig. 3); in other parts it was astrocytic in nature. It was most pronounced in the occipital, temporal and parietal regions, less marked in frontal regions. It was mostly perivascular and patchy in extent, but there were also wide stretches of a continuous glial felt.

There was practically no indication of the severity of the process in the myeline picture.

In Nissl pictures nothing was seen except the proliferation of the macroglia; but as a whole they did not indicate the severity of the glial process. Within the globus pallidus a moderate degree of pseudo-calcium was found, showing, as usual, a marked iron reaction. There was little to say regarding other details.

All slides showed a marked hyperæmia.

Fat stains revealed only occasionally some ordinary lipoid inclusions in perivascular scavenger-cells.

There was no gross cyto-architectonic disturbance of cortical and other grey areas with the exception of the dentate nucleus, in which many nerve-cells showed Nissl's chronic change. The fibrous gliosis was here particularly heavy, without any mentionable outfall of myelin fibres and axis cylinders.

Case 3.—M. J. A—, male, aged 10 months. Admitted to Fountain Hospital 16.x.35.

Family history.—The patient was the second of two children, the other being mentally and physically healthy. The father was aged 34 and the mother 33 years at the time of his birth. The mother was healthy, but the father was stated to be suffering from gastric trouble.

History of gestation and birth.—The father was stated to have been invalid at the

* History given from a paper by L. C. Cook: "Amyoplasia Congenita associated with Mongolism" (1936).

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time of conception. During the second month of pregnancy the mother had a severe fright. Throughout pregnancy she was in a very worried state as her husband was in hospital with gastric trouble. The labour was "rather precipitate". No other details were available.

Developmental history.—Abnormality was noted soon after birth. The baby never sucked properly, never made an attempt to sit up, cried incessantly, and took no interest in any object normally attractive to a child of this age. He never talked. He cut one tooth after admission to hospital.

Physical condition.—A typical mongol baby. No abnormality was noted in the nervous system.

Mental state.—He was unable to lift up his head at the age of 10 months, or to sit up unsupported. He would not reach out for a brightly coloured object.

On 22.ii.36 he developed signs of bronchitis, in association with the cutting of a tooth. The bronchitis improved, but he died suddenly on 30.iii.36.

Post-mortem examination showed early broncho-pneumonia. There was congenital heart disease present. Patent foramen ovale with a defective interventricular septum.

Macroscopic examination of the brain.—This brain, which had previously been fixed in formalin and cut, was very soft and distorted. On naked-eye inspection no thickening of the meninges or blood-vessels was seen. There was no obvious discrepancy between the size of the brain-stem and the rest of the brain. The convolutional pattern showed no signs of malformation. There was little evidence of any changes macroscopically. The weight of the brain was not recorded.

Histological examination.—The results of nearly all the staining methods, particularly those of a higher differential character, were not wholly satisfactory, owing perhaps to faulty fixation. It was, therefore, difficult to assess the extent of the fibrous glia proliferation. There was no doubt, however, that the glia proliferation in sub-ependymal areas, particularly that of the posterior (Fig. 4) and inferior (Fig. 5) horns, surpassed the normal range. There seemed to be—even beyond this localization—marked perivascular sclerosis throughout the white matter, as far as it could be ascertained.

With higher magnification the gliosis appeared as a dense network with astrocytes interspersed (Fig. 6). The gliosis was often accentuated in the neighbourhood of blood-vessels.

The myelin picture, apart from some rarefaction, showed very little change.

In Nissl pictures the proliferation of the macroglia was obvious, and also swelling of the oligodendroglia was seen. By the Herxheimer method accumulation of granular compound cells loaded with fat were often seen in the vessel sheaths.

The cortex, as a whole, was preserved, though the extreme softness of the material did not produce adequate pictures of the ganglion-cells, which throughout showed Nissl's " water change ".

Possibly for the same reason the myelin picture of the cortex was not very satisfactory.

No neuroblasts were seen, although the number of heterotopic ganglion-cells in the white matter was greater than was normally to be expected.

In the cortex and white matter endothelial swelling was often seen.

The brain-stem was unaltered except for some slight gliosis below the floor of the fourth ventricle and in the white matter of the cerebellum.

The Purkinjē cell apparatus and granular layer of the cerebellar cortex were normal to all appearances.

Owing to previous dissection the midbrain and diencephalon could not be fully examined.

CASE 4.—L. C. H—, male, aged 3 years 8 months. Admitted to Fountain Hospital 11.iii.27.

Family history.—The patient was the youngest of four children. The other three children were healthy. The father was 40, the mother 37 years old at the

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time of the patient's birth. There was a history of epilepsy and chorea on the mother's side. The labour was stated to have been normal.

Developmental history.—The patient walked at 2½ years, and talked at 3 years. Teething began at 9 months. He had whooping-cough and chicken-pox before admission to hospital.

Physical condition.—He presented mongolian features, with the facies, slight epicanthus, blepharitis, hypotonia and lax joints. His circulation was poor, as shown by his cyanosed limbs.

Mental state.—He was an imbecile, unable to speak apart from one or two simple words, unable to understand or do anything for himself, and faulty in his habits. On 17.i.28 he developed measles, and died of broncho-pneumonia three days later.

Post-mortem details unfortunately were not available.

Macroscopic examination of the brain.—The brain was small, with no obvious abnormalities of pattern. The white matter in many regions was suspect because of some slight grey-yellowish appearance. Nothing else worth mentioning was seen. The brain weight was not recorded.

Histological examination.—The staining with more highly differential stains was not satisfactory. With Holzer stain the glial proliferation of the white matter could be seen even macroscopically (Fig. 7). Microscopically many areas in all cerebral white matter regions were found to contain a fibrous gliosis of a patchy nature, often pronounced around blood-vessels with thickened walls (Fig. 8).

There was little change to be reported in the cerebral cortex ; some increase in the subpial glia ; the cell layers were somewhat irregular and the position of the ganglion-cells often incorrect. Unfortunately the cortex was rather damaged in the slides and did not decolorize properly.

There was marked gliosis in all subependymal regions and, in addition, in the nuclei pontis, olivary body, other parts of the medulla and the cerebellar white matter.

The number of ganglion-cells in the olive was definitely diminished.

There was no sclerosis of the cornu ammonis. No gliosis in the principal hypothalamic nuclei, no fatty breakdown products and no changes of axis cylinders, which were preserved throughout as far as the staining permitted one to say.

CASE 5.—D. C. M—, male, aged 11. Admitted to Caterham Hospital 13.v.27.

Details of family history, birth and early developmental history were not available.

Physical condition.—A typical mongol. No abnormality was discovered in the heart or nervous system. The Wassermann reaction of blood and cerebro-spinal fluid was negative.

Mental state.—An idiot, he was unable to speak and incapable of responding to simple commands. His activities consisted of rocking movements, thumb-sucking and making rhythmic movements of his hands over a period of hours.

He was wet and dirty in habits. His general health remained fairly good until 5.iv.37, when he developed signs of pulmonary tuberculosis. He died on 13.iv.37, at the age of 21 years.

Post-mortem revealed patchy broncho-pneumonia of both lungs, tuberculous in nature. The right pleura was obliterated with old adhesions.

Macroscopic examination of the brain.—The brain was rounded in shape and weighed 1,212 grm. The pial vessels were definitely injected. No discrepancy between the size of the cerebellum and brain-stem and rest of brain was found.

On section the white matter in the occipital region presented a brownish colour.

Histological examination.—With Holzer stain there was a dense felt of proliferated fibrous glia within the occipital and temporal regions, near the ventricle, but also somewhat remote from it. Microscopically there was found throughout the cerebral white matter a mobilization of the macroglia, which was hypertrophic and the cells increased in number. The cortex was, as a whole, left free, with the exception of a subpial glial fibrosis, often very marked.

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The myelin picture showed no indication of the process. In Nissl pictures the amount of macroglia was also definitely increased in those regions which showed gliosis.

The cortex appeared normal in Nissl pictures. There were no signs of recent breakdown products apart from an increased number of pigment-carrying macrophages around some vessels. Fat-staining lipoids were scanty.

The globus pallidus contained a considerable amount of pseudo-calcium.

Around the aqueduct (Fig. 9), in the nuclei pontis, the olivary body (Fig. 10) and white matter of the cerebellum the gliosis was particularly marked, without definite change in the myelin-stained slides. Considerable fibrous gliosis was also seen within the supra-optic nucleus without appreciable outfall or change of the ganglion-cells.

In Nissl pictures there was a slight diffuse loss of ganglion-cells in the olive, the remaining cells showing much pigment atrophy.

Glial proliferation was also found diffusely in the medulla.

CASE 6.—G. P—, male, aged 7. Admitted to Fountain Hospital 28.i.21. Later transferred to Caterham Hospital, 5.ix.22.

Family history.—He was the youngest of seven children. The mother was 52 and the father 52 years at the time of the patient's birth.

History of gestation.—The mother is stated to have suffered bad health throughout pregnancy. She is reported to have had a severe fall four days before her confinement. The history of the labour is incomplete. The patient was thought to be dead and had to be stimulated. He did not cry, slept a great deal, and would not take the breast for the first two days.

Personal history.—When 6 months old he fell on his head. Teething is reported to have been "early". He walked at the age of three years. He never talked beyond a few monosyllables.

Physical condition.—He presented typical mongolian features with marked epicanthus, large fissured tongue, and characteristic hands and feet. No abnormality was discovered in the heart or nervous system. The Wassermann reaction of blood and cerebro-spinal fluid was negative.

Mental state.—A low-grade imbecile, he was unable to read or write or to wash or dress. He fed himself. His general health was always poor. On 20.iv.24 he developed measles. On 9.v.24, while recovering from measles, he passed loose motions with blood and mucus. He lost a lot of weight. He recovered and remained fairly well until 25.i.29, when he again passed loose motions, and one week later developed signs of broncho-pneumonia. The lung symptoms cleared up, but his motions remained loose over a period of two months. His fæces were repeatedly examined, but no tubercle bacilli were found. Examinations of the motions for typhoid and dysentery were also negative.

He recovered and remained in fair health until 19.i.34, when he again developed a temperature and passed loose motions. Tubercle bacilli were now recovered from the motions. He died on 3.ii.34 from tuberculous enteritis, at the age of 20 years.

Post-mortem.—Signs of old tuberculosis of the lung. Active tubercular ulceration of intestines. No evidence of heart disease.

Macroscopic examination of hardened brain.—The weight of the brain was 1,134 grm. There were no abnormalities of proportion apart from some ill-defined smallness of the first temporal convolution.

On coronal section various parts of the white matter of the cerebrum and cerebellum were seen to be of a slightly brownish colour.

Histological examination.—There was in Holzer pictures considerable fibrous gliosis within the white matter of the occipital and temporal lobes, and to a lesser degree in the frontal lobe.

The gliosis around the "keel" of the posterior (Fig. 11) and inferior horns certainly exceeded that to be expected under normal circumstances. There was

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also much proliferation of fibrous glia in regions of the white matter remote from the ventricular surfaces. It was either of a dense type, poor in cells, or astrocytic in type and in a perivascular situation.

The glial proliferation often gave the impression of being rather recent. In Nissl pictures this was particularly distinct. In parts the macroglia was distinguished by the enlargement of the nucleus, which was very pale, and contained increased chromatin, and by the visibility of the processes and cytoplasm.

In other parts the gliosis was certainly of old standing. There was very marked gliosis in the pons (round the aqueduct, within and around the nuclei pontis), the medulla (olivary body and diffuse in other parts), the white matter of the cerebellum, all sub-ependymal regions, etc.

Both dorsal to the optic tract and within it there was also marked increase, but the supra-optic nucleus, like the other principal hypothalamic nuclei, appeared not to be involved. Detailed systematic examination is yet to be done.

There was generally marked subpial sclerosis, particularly severe in the insular region. The external capsule and lamellæ of the globus pallidus were also slightly sclerosed.

The myelin picture was normal.

In Nissl pictures, apart from the glial changes already mentioned, the cyto-architectonic structure was as a whole preserved. There was some outfall of ganglion-cells in the olivary body and dentate nucleus and here and there of Purkinjĕ cells.

Fat pictures showed only a negligible amount of lipoid in the vessel sheaths.

No heterotopias or other sign of arrest of development were seen.

CASE 7.—V. B—, female, aged 3 years 1 month. Admitted to Fountain Hospital 11.ii.30.

Family history.—She was the youngest of six children. The father was aged 47, the mother 45 at the time of the patient's birth. The father was in good bodily health, but the mother is stated to have been frail. The gestation was marked by much sickness. Two frights to the mother occurred about the time of quickening. The fœtal movements were described as being "short, quick and rare". There was a history of ante-partum hæmorrhage. The labour lasted seven hours, and the baby was born by a breech presentation.

Personal history.—The patient never walked or talked previous to admission. She had suffered from measles, whooping-cough and chicken-pox. Later after admission she contracted scarlet fever.

Physical condition.—A typical mongol, with well-marked signs of congenital heart disease. She was always cyanosed, and on slight exertion or emotion she became purple in colour. She suffered at times from "heart attacks", when she became profoundly cyanosed and dyspnœic and developed twitching movements, mainly affecting the arms. The attacks lasted about a quarter of an hour.

The fingers were markedly clubbed, and there was evidence of chronic bronchitis.

Mental state.—She was an imbecile, who on admission could not speak or walk, was faulty in habits, and required every form of attention. Later she could speak a few words and could walk fairly well.

She became ill with signs of pulmonary congestion on 1.iv.35, and died on 15.iv.35 from broncho-pneumonia.

Post-mortem.—The heart weighed 4½ oz. The left ventricle was hypertrophied. The pulmonary valve was markedly stenosed. There was a very large patent foramen ovale. The liver was enlarged and of the cardiac type. There was a large empyema with collapse of the lung on the left side and right-sided broncho-pneumonia. The brain weighed 1,008 grm. No abnormal macroscopic features were detected.

Macroscopic examination of the brain.—Only one hardened hemisphere and half of the stem was available for investigation.

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There were no abnormalities of the convolutional pattern, and as far as could be ascertained, of the proportion between stem and hemisphere. On coronal section the white matter in the occipital, temporal and frontal regions was slightly mottled in appearance because of the hyperæmic blood-vessels.

The cerebral and cerebellar cortex were normal.

Histological examination.—In the occipital and temporal regions there was a marked degree of diffuse and patchy glial fibrosis. It was also found in the frontal regions, and was particularly severe in the regions near the ventricle, which were fibrosed throughout.

The myelin picture was normal throughout except for shadow foci near the ventricular surface similar to those described by Davidoff. They did not contain, however, any fatty products in phagocytic cells.

The ventricular gliosis was also marked round the third ventricle, aqueduct and fourth ventricle.

In the cerebellar white matter there was some gliosis of a perivascular character, but there were also wide stretches of a dense glial felt. This was particularly severe in the hilum of the dentate nucleus.

In the medulla the hilum of the olivary body was gliotic, as was also the floor of the fourth ventricle.

In the Nissl picture the macroglia cells appeared increased in number. There was a diffuse hyperæmia, which was particularly marked in the cerebellum.

Around some of the vessels exhibiting perivascular gliosis recent hæmorrhages were seen.

In the cerebral cortex the molecular layer was rather large. The stratification and appearance of the nerve-cells was, however, undisturbed.

The number of nerve-cells within the cerebral white matter was somewhat larger than normal.

In the globus pallidus enormous amounts of pseudo-calcium which gave a strong iron reaction were present. The precipitations were in the walls of medium-sized vessels and capillaries, but also lying free.

There was no melanin in the substantia nigra, though the number of ganglion-cells of the compacta was normal.

The ganglion-cells of the olivary body, dentate nucleus and cerebellar cortex showed no abnormalities.

CASE 8.—G. H—, male, aged 17. Admitted to Leavesden Hospital 21.viii.35.

Family history.—The patient was the youngest of four children, and there was an interval of twelve years between his birth and the previous child. No other history regarding his birth was available.

Physical condition.—He presented typical mongolian characteristics. No evidence of any cardio-vascular disease was present. The nervous system was healthy.

Mental state.—He was an imbecile of low grade. Sullen and morose and subject to fits of bad temper. He refused to co-operate in any way. His speech was indistinct. He was unable to wash or feed himself.

On 23.vi.36 he developed signs of acute appendicitis. On 25.vi.36 he was operated on, when a large pelvic abscess was drained. He died on 26.vi.36, after an illness of three days. Post-mortem notes were not available.

Macroscopic examination of the brain.—The brain was rounded in shape, with no narrowness of the interpeduncular space, and no disproportional smallness of the brain-stem. There were no abnormalities of the convolutional pattern. The weight of the brain was not available.

Histological examination.—There was a focal excess of fibrous glia only in a few cerebral and cerebellar white matter regions. There was, moreover, a definite slight gliosis in the lamellæ of the globus pallidus, in the pons and in the medulla, chiefly in the olive.

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The Hallervorden-Spatz pigment in the globus pallidus was slightly increased in amount. There was a definite outfall of ganglion-cells in the olivary body. The myelin, Nissl and Scharlach R pictures showed no significant change.

CASE 9.—K. F. H—, female, aged 5 years 7 months. Admitted to Fountain Hospital 23.vi.23.

Family history.—The patient was the second of three children, the other two being mentally and physically normal. The parents were unrelated; the father was 38 and the mother 34 years at the time of the patient's birth. The mother was reported to be "nervy" as a child and "very clever". She later committed suicide 5½ years after the patient's birth.

Personal history.—The birth was reported to have been normal, no instruments having been used. Abnormality was noted from birth. The patient never developed properly. She walked at 18 months, teethed at 12 months, and never talked properly.

Physical condition.—She was a mongol of poor physique, with well-marked epicanthic folds, blepharitis and conjunctivitis. The tongue was large and slightly fissured. No abnormality was noted in the cardio-vascular system. There was no sensory loss. There was marked hypotonia and laxity of the joints. The secondary sexual characteristics were present.

Mental state.—She was an imbecile, unable to speak, but capable of responding to simple orders. She showed no recognition of simple objects. Her habits were faulty.

On 29.viii.35 she developed signs of right-sided pleural effusion, with a rise of temperature in the evening to 100°. Notified as pulmonary tuberculosis on 13.ix.35. On 29.x.35 she was sent to Leavesden Hospital. Gradually getting worse, she died on 9.iii.36, after an illness lasting over 7 months.

Post-mortem examination showed a grossly thickened pleura on right side with total obliteration of pleural cavity. There were miliary tubercles in both lungs and early tubercular peritonitis with tubercles in both kidneys.

Macroscopic examination of brain.—No abnormality worth mentioning was seen. The brain weight was not recorded.

Histological examination.—There seemed to be an increase of glia in all sub-ependymal regions, though it was difficult to say whether this much surpassed the normal range. The subpial glia was, however, pathological.

No definite gliosis was seen in the cerebral white matter. Much gliosis was found, however, in the pons, medulla, and particularly in the white matter of the cerebellum (Fig. 12), again without demyelinization.

Nissl pictures showed all cortical regions to be fairly normal except for frequent disturbances of the position of the mature ganglion-cells. In the globus pallidus a slight increase of Hallervorden-Spatz pigment was found. The olive showed a slight diffuse diminution of the nerve-cells, and a marked increase of macroglia, the latter was also seen in the dentate nucleus.

The cerebellar cortex was fully preserved in Nissl pictures.

CASE 10.—M. G. J—, female, aged 13. Admitted to Caterham Hospital from Fountain Hospital on 15.viii.22.

Family history.—She was the last of ten children, the mother being 45 and father 46 years old at the time of her birth. The mother's pregnancy and labour were reported as being normal, but the birth was premature, occurring at the eighth month.

Physical condition on admission.—A typical mongol in fairly good health, but with poor circulation. No definite abnormality was noted in any system.

Mental condition.—She was a low-grade imbecile, able to answer only the very simplest of questions. She was able to feed and dress herself, but required general

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supervision. She was mischievous, and often destructive to clothing. She performed simple routine work, such as ward polishing. Her medical history since her admission is as follows:

On 21.iv.24 she contracted measles, from which she recovered completely. On 12.iii.28 there is first mention of glandular enlargement of submaxillary area, which subsided after two weeks. On 20.iv.29 she was recovering from a mild attack of dysentery (Flexner). The course was afebrile throughout.

The Wassermann reaction was performed as a routine examination on 31.xii.32. Result: Blood—Wassermann reaction negative; Meinicke negative. Cerebro-spinal fluid—Wassermann reaction negative. Cells + (lymphs.), protein +, Lange 5554321000.

This test was repeated on 27.xi.34, i.e., two years later. Blood—Wassermann reaction negative; Meinicke negative. Cerebro-spinal fluid—Wassermann reaction negative. Cells negative, protein +, Lange 55554443210.

On 30.i.36 she was in bed with temperature of 99°–100° with a slight evening rise. Diagnosed as broncho-pneumonia. No tubercle bacilli were found at this time on examination of fæces. No sputum was available. She recovered from this attack completely by 20.ii.36. Almost exactly a year later, on 22.i.37, she became ill again with signs of acute bronchitis, from which she again recovered.

On 5.iv.38 enlarged painless glands were found in neck and in both axillæ (one in each axilla). Biopsy of this gland showed giant-cells of the Langerhans type, caseation and presence of tubercle bacilli. The temperature, pulse and respiration were not raised. On 9.vi.38 cough was present, there was pyrexia of swinging type and bronchial breathing in the chest with widespread crepitations. She rapidly became worse, with increase of broncho-pneumonia, and died on 29.vi.38 at the age of 29 years.

Post-mortem.—The post-mortem examination was carried out 19 hours after death. The brain weighed 998 grm. It was small and rounded in shape. The cerebellum and brain-stem were small compared with the rest of the brain. The first temporal convolution on each side was narrow. The vessels of the brain and of the meninges appeared normal. On coronal section the dentate nucleus in each half of the cerebellum was very soft and reddish-brown in colour. Both lungs were studded with patches of caseous broncho-pneumonia. Miliary tubercles were also present, and small cavities in the apex of the left lung. Enlarged caseous bronchial glands were present. The heart was small, the muscle fatty. No evidence of congenital heart disease was found. In the abdomen numerous large egg-shaped caseous glands were found in the mesentery and in the para-aortic region.

Histological examination of the brain.—Numerous small patches of demyelinization were found in the white matter of the cerebellum, often sub-ependymal, and occasionally near the dentate nucleus and in the medulla and spinal cord. They were often rather sharply demarcated, particularly in the cerebellum. In the spinal cord and medulla, however, the borderline was for the most part hazy. Within these areas heavy fibrous gliosis was found. There was also a considerable amount of lipoid in glial and adventitial cells, and occasionally in granular compound cells. The axis cylinders were better preserved, as seen in Bielschowsky-stained sections. Within the demyelinized area there was some inflammatory reaction. Beyond these focal lesions there was considerable diffuse fibrous gliosis in the pons and in all sub-ependymal regions. Otherwise no changes of any significance were seen. This case will be fully described in another place later.

Discussion.

Although evidence of a pathological process has been found in a considerable number of our cases, the absence of such lesions in the remainder makes it impossible to regard these changes as a substrate of the mental defect in

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mongolism. We are thus confronted with the task of seeking for the causes, accidental or not, which have produced them. Before we do this it is necessary to determine the histological nature of the changes.

Some of the changes, such as the sub-ependymal or other foci of demyelinization, and the frequent finding of pseudo-calcium in the globus pallidus, resemble closely the findings of Davidoff (1928), who attributed to them a considerable pathogenic importance, as we shall have to discuss later.

The demyelinized foci in the last case (No. 10) resembled closely the early patches of disseminated sclerosis. The demyelinized areas were marked off rather sharply, and there was a considerable preservation of axis cylinders. We must leave open the question as to whether these areas represent a complication with early disseminated sclerosis, or whether they are related to those foci of demyelinization described by Davidoff, and which were also seen in some of our other cases.

Apart from these changes, widespread proliferation of the fibrous glia was a surprisingly frequent feature. As a rule it did not correspond to any serious breakdown of parenchyma. The overgrowth was particularly noted in the cerebral and cerebellar white matter and in the pons and medulla. It was either diffuse as in Case 1, or it was circumscribed. In some cases it formed only an intensification of the fibrous glia normally found along the outer and ventricular surfaces, and in centres such as the olivary body and dentate nucleus.

The appearance of the fibrous glia varied. It might be a dense felting poor in astrocytes, or merely an increase in number of the astrocytes. Occasionally it showed by Nissl and other staining reactions the signs of recent formation, as in Case 6, but even in this case older glial scarring was also present. A distinctly perivascular nature of the gliosis was often seen. Only in our last case were fatty products found in sufficient quantity to deserve mentioning. This last case, as has already been said, needs special consideration.

The glial overgrowth was best seen with Holzer staining. Various Hortega modifications have been employed, but as a whole they did not add essentially to what was seen in Holzer and Nissl slides.

There is no evidence that the glial changes can be regarded as a sign of maldevelopment. They are in all their characteristics identical with those occurring in ordinary disease processes, nor was there any evidence of a blastomatous overgrowth of glia, such as occurs in tubero-sclerosis, Recklinghausen's disease, and related processes. Nevin (1938) has recently described a condition which he has called "gliomatosis cerebri". None of the irregularities of glia-cells which he described were noted in our cases.

Apart from purely negative statements it is very difficult to come to a clear decision as to the nature of the changes. Fibrous gliosis with little or no demyelinization has been recognized in recent years as a special type of affection

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of the white matter (Bodechtel and Guttmann (1932)). Studies of the brains of mental defectives have led Meyer and Cook (1937) to the conclusion that it is a frequent occurrence in low-grade defectives with or without gross neurological disturbances. Bodechtel (1932) has found that in congenital heart disease the white matter is particularly vulnerable, whereas in heart disease of adults the cortex is more prone to lesion. Schwartz (1924) stressed the vulnerability of the white matter in birth injuries. The occurrence in mongols of a patchy gliosis often around blood-vessels, of circumscribed sub-ependymal softenings, and in one case apparently uncomplicated with epilepsy of a typical sector sclerosis of the cornu ammonis, makes one think that a vascular factor or other interference with the oxygenation of the tissue might be instrumental in the production of these changes.

It is useful to consider in this connection the white-matter changes produced by poisoning with carbon monoxide and cyanide of potassium, though the lesions produced by these poisons are not only confined to the glia. These poisons act by way of interference with oxygenation. One of the present writers (Meyer, 1938) has recently endeavoured to compare the gliosis in the brain with the fibrosis in other organs following a mild stasis of long standing.

If, then, a vascular or some other kind of anoxic factor has to be seriously considered as the cause of the changes found in our mongol cases, it is well to emphasize that this interpretation is only advanced tentatively ; moreover, we have to consider that interference with oxygenation may be secondary to any toxic or infectious process. Thus the range of ætiological possibilities remains very wide.

It is with these considerations in mind that we have to look for possible causes of the changes. Naturally we have to consider first whether the terminal disease could account for the changes. A review of the clinical history in comparison with the histological appearances showed that in at least six cases of the material presented this was extremely unlikely, because with full recognition of the difficulties of estimating the age of brain lesions (Müller (1930)) it was thought impossible that the lesions could be produced during the relatively short terminal disease ; in some cases death occurred suddenly. This applies to Cases 1, 2, 3, 4, 7 and 8. In the four other cases the terminal disease could be considered seriously at least as one factor instrumental in producing the changes. Incidentally these latter cases all died from chronic tuberculosis of the lungs and bodily organs. Tanaka (1936), in a paper which unfortunately was only available to us as an abstract, has recently drawn attention to the occurrence of fibrosis of the meninges, ganglion-cell changes, increase of fat and slight glial and myelin change in cases of severe organ tuberculosis. Even so the occurrence of heavy proliferation, such as in Case 6, or the unusual appearances in Case 10 (if we leave a possible complication with disseminated sclerosis out of consideration), remain doubtful as to their causal relationship with tuberculosis.

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In view of Bodechtel's (1932) findings, attention has been paid to congenital heart disease, which is a rather frequent accompanying symptom in mongolism. Yet congenital heart disease was absent in Cases 1, 2, 4 and 8, though in Case 2 the finding of an unusually large heart is reported, and in most of the cases a poor peripheral circulation has been recorded which is frequent in mongolism even in the absence of manifest congenital heart defect. It is striking that Case 1, which showed the severest and most general change, had no heart defect. In this case premature and protracted labour is reported, though not more than a surmise can be based upon the birth history, which was very poor. Difficulties during pregnancy and at birth are also reported in Cases 2, 3, 6, 7 and 10. We mention this because recently it has been found that the number of premature births and hæmorrhages during the pregnancy of the mother is surprisingly large compared with normals (H. Schroeder (1938)).

Thus we are at a loss to discover any factor common to all cases which would account for the changes found in a relatively large percentage of our material. The conclusion is that either this common factor is not known, or the changes are due to causes varying in the individual cases.

The clinical histories of our cases are not complete enough to arrive at a clear decision upon this point. Mongols are known to be easily susceptible to any infectious or toxic damage, and are generally believed to have a poor circulation. They often die young because of their lack of resistance to infection or over-strain of the circulatory system. It is quite possible that any such attacks during their lifetime, even if they do not end life, may leave their marks on the brain.

The foregoing considerations may lead to a better understanding of the lesions described by previous workers. Most of these investigators discussed the changes in the brain as an expression of the pathological process underlying mongolism. Even Davidoff, who excluded minor changes as accidental, was inclined to regard the sub-ependymal foci as remnants of a pre-natal degenerative process responsible for the defect in mongolism. From what has been said above, great reserve is necessary in submitting such far-reaching conclusions. Our material, which represents a wider variation in length of life than that of Davidoff, shows that relatively recent changes may be found, even in cases which die in the third decade of life. It is, therefore, likely that all such changes must be regarded as accidental to the pathology of mongolism. Whether their significance is exhausted by this statement is a different question. It may well be that the incidence of pathological changes is greater in mongolism than in other conditions, owing to the peculiar constitution of the mongol. One might even assume that the same functional abnormality underlying mongolism produces also the histological changes which, though constant, would obtain a certain significance as indicator of the pathogenesis of mongolism; but this is at present purely speculative. We do not know enough about the reaction of the brain to bodily diseases, especially in infancy and

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childhood, and we are therefore not in a position to decide whether this reaction is more severe in mongols than in other groups of defectives and normals. Wertham (1934), in another connection, has already drawn attention to the general lack of normal controls.

Systematic controls will therefore be necessary before a real appreciation of the brain findings in mongols will be possible. Investigations in this direction are in progress in this laboratory.

Consideration was given to the possibility that the frequently found small size of the brain-stem and cerebellum, and occasionally of one of the temporal convolutions, might be due to the scarring in these parts rather than to arrest of development. It was found, however, that there is no consistent correlation between the size of these parts and the degree of glial scarring, though it is conceivable that the glial scarring, if severe, might contribute to the smallness of size.

Our results may give rise to two final considerations. Mongols are considered to be "able-bodied" and lacking gross neurological symptoms. It would not be surprising, however, to find neurological symptoms more frequently. Careful neurological investigation might also be helpful in determining the exact date of onset of the brain lesions, thus aiding considerably the interpretation of the histological changes.

Secondly, the investigation has demonstrated how erroneous comparative work based on measurements of cyto- and myelo-architectonics alone might be. Such comparative studies are necessary, but they must include a complete histological analysis, if grave errors are to be avoided.

Summary.

Ten cases, out of a total material of 15 cases, are described in which the histological examination of the brain revealed remarkable changes, consisting mostly of widespread proliferation of the fibrous glia, which very often was not accompanied by corresponding changes in the myelin and cell picture. The pathogenesis of the changes is discussed, and it is shown that the findings are not likely to represent the pathological substrate underlying mongolism. They throw light, however, on the interpretation of findings reported by previous writers.

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