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CONTRIBUTIONS TO THE PATHOGENESIS OF MONGOLISM

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Mongolism is a peculiar phrenasthenic biopathy associated with pluriglandular insufficiency manifesting itself, apart from a number of facultative characteristics, in a complex of symptoms comprising obliquely set (mongoloid) eyes, oligophrenia, microcephaly, muscular hypotony, and a disproportionately built body.

This uniformity of the traits of the syndrome make most cases look like siblings.

The identical appearance of the disease in almost every case suggests a common aetiology.

While the question of causation is still debated, observations keep accumulating in which the possibility of a chromosome anomaly is considered in this disease [1, 2, 3]. Such considerations imply an approach to the cause through the laws which govern the chromosome-enzyme system. This is a point which has been raised before in the literature [4, 5, 6, 7, 8].

The pathogenesis of the disease is unknown, and attempts to throw some light upon the problem are here presented, which are based upon a study of the chain of morphologic transformations resulting in mongolism.

There is agreement in that the brain of patients with mongolism weighs less than that of the average individual of the same age [9, 10, 11, 13, 12, 14]. However, one of the invariably present typical features of the disease is microcephaly. We have been unable to find any data in the literature discussing microcephaly as a symptom associated with mongolism.

Head circumference is generally expressed in relation to age. The authors studying it in mongolism seem to have been misled by the retarded somatic growth in that condition. They have accepted the small skull with the thought that nanosomia, too, is a characteristic feature of the disease. The fact, however, is that where the head circumference of a patient is compared not with that of a nanosom but a normal individual of the patient's height, it will be found considerably less, occasionally by as much as 5 to 6 cm. Fig. 1 compares the head circumference of 52 patients with mongolism of either sex in different age groups with that of normal individuals of corresponding body height.

Deranged chondrification of the cranium primordiale, in other words, retarded proliferation of cartilage cells at the base of the skull, appears to be responsible for the characteristic shape of the skull. The base of the skull being shortened, the cranium changes in shape and at the same time microcephaly develops. This may lead, secondarily, to progressive compression of

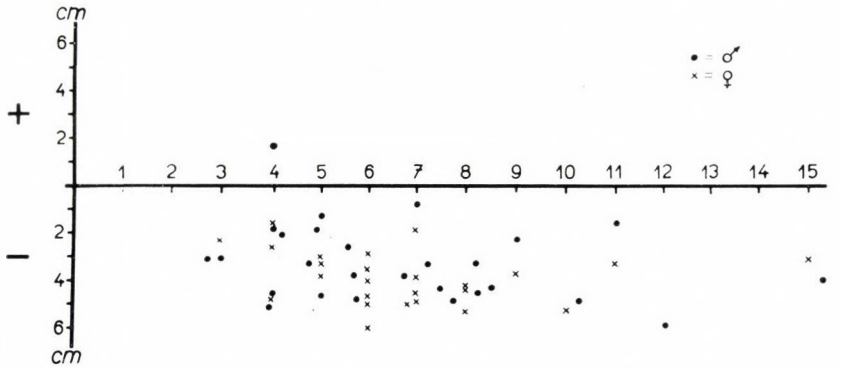

Fig. 1. Head circumference of 52 patients with mongolism of either sex in different age group and of normal individuals of corresponding body height

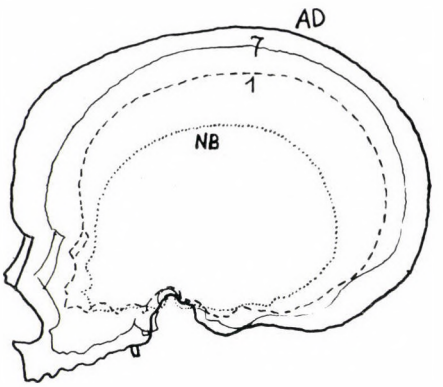

Fig. 2. MERKEL and HASSELWANDER's diagram illustrating skull growth in the sagitta plane. NB = newborn; AD = adult; the numbers express age in years

the brain, the primary cause being probably arrested growth of cartilage between the sphenoid and occipital bones, which are known not to unite in some cases until about the 20th year.

CLARA [15] and TÖRŐ [16] both point to sphenooccipital synchondrosis as the condition which ensures growth of the base of the skull in the sagittal plane. A clear and vivid conception of the dynamics of this growth is given in MERKEL and HASSELWANDER's diagram (Fig. 2).

Notwithstanding the attention STOCKARD [17] had devoted to the point as far back as 1916, INGALLS [12] thirty years later deplored the paucity of data in the literature concerning the normal development of sphenooccipital synchondrosis. Insufficient histological and radiological evidence has since accumulated to give us a full understanding of the formation of this important epiphyseal plate.

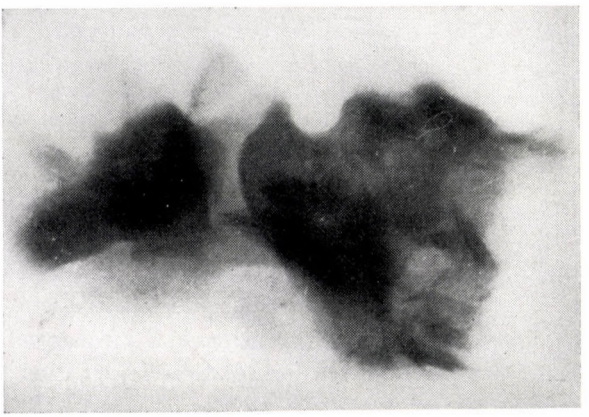

Fig. 3. X-ray of the sphenooccipital complex of a newborn

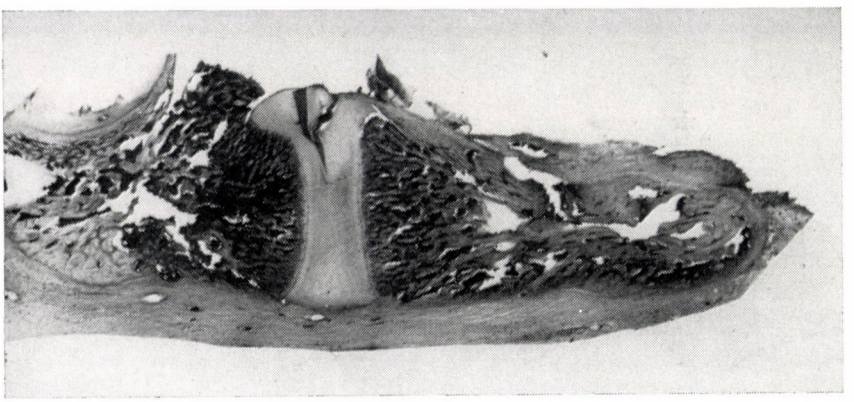

Fig. 4. Frozen section in the midsagittal plane of the complex shown in Fig. 3 (×5). Cartilage of the sphenooccipital synchondrosis seen in the centre

It was with the foregoing as background that we subjected the sphenooccipital synchondrosis to a detailed study, though it is not the only area of the skull to secure postnatal sagittal growth of its base.

Our observations seem to suggest the conclusion that the sphenooccipital synchondrosis is an epiphyseal plate with one of the proliferative zones facing the sphenoid bone and the other the basilar part of the occipital bone. Inter-

preting sagittal skull growth in a functional sense, this means that the sphenooccipital complex develops as a single bone with the sphenoid its "epiphysis" and the basilar part of the occipital its "diaphysis" (Figs. 3 and 4).

Like every other epiphyseal plate, the sphenooccipital synchondrosis depends for its normal development on genetic, hormonal and vitamin factors. The question arises which of these is the preponderant factor in the pathogenesis of the deformity of the head in mongolism.

It is difficult to attempt a general comprehension of the development of the skull in this disease, for most of the autopsied cases are premature and young infants and most of the published data refer to such cases. Nor can one rely on X-rays for exact information: either the spinal column or the pars petrosa projects itself into the picture of the sphenooccipital synchondrosis, adversely affecting evaluation.

GREIG [18] speaks of a precocious ossification of this cartilaginous junction in mongolism. In the light of our investigations one should think of inhibited proliferation rather than precocious ossification.

Inhibited proliferation of cartilage can be the result of genetic factors, but hypothyroidism, syphilis and vitamin A deficiency during pregnancy are equally capable of producing it (WOHLBACH and BESSIE, 19].

According to WEATHERFORD [20] the disease begins from the sixth to the ninth week of embryonic life when the sphenooccipital synchondrosis starts differentiating, and from this he infers, as does INGALLS, that the cause is embryopathy.

At the said stage of uterine life the embryonic cartilage actually resembles the somatic developmental stage in mongolism. This is well illustrated by HAGEN's reconstruction model of the chondroskeleton of a 17-mm human embryo.

On similar considerations, chondrodystrophy, too, would have to be regarded as of embryopathic origin since at a certain stage of the limbs, development of the foetus displays relative micromelia and an elevated calvary, i. e. in body proportions it greatly resembles the chondrodystrophic dwarf.

Yet, who would be likely to conceive of chondrodystrophy as a syndrome of embryopathic aetiology?

For the clinodactily of the little finger seen in mongolism both BENDA [11] and INGALLS [12] offer the explanation that the underlying lesion affects the foetus at the time the mesophalanx is in the process of differentiation. This differentiation actually coincides with that of the cartilaginous base of the skull.

It should be noted that clinodactyly is only a facultative symptom of mongolism, indicating in about 35 per cent of the cases that chondrification and ossification are irregular and defective. One of its causes is always the inadequately directed proliferation of the epiphyseal plate of the mesophalanx

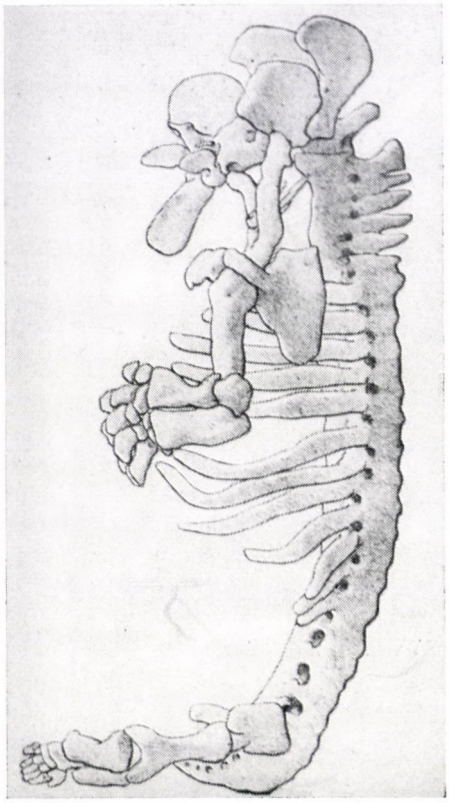

Fig. 5. HAGEN's reconstruction model of the chondroskeleton of a 17-mm human embryo

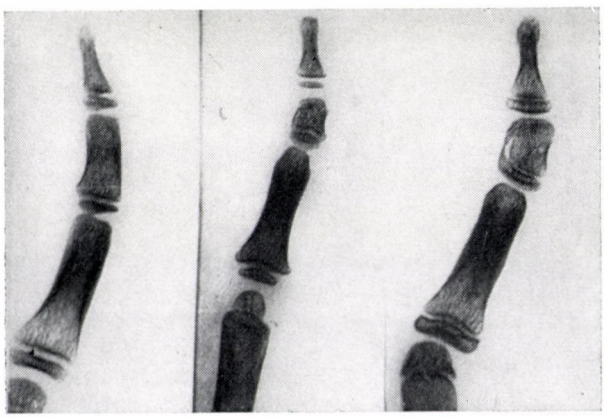

Fig. 6. X-rays of the little finger of three children with mongolism

(Fig. 6). Acromicria is produced in a similar manner; so is a shortened femur [21], which is a symptom invariably present in mongolism.

The conclusion is that mongolism is characterized by chondral dysostosis invariably affecting skull and femur formation, and sometimes the epiphyseal plates (mesophalanx) in the other parts of the body.

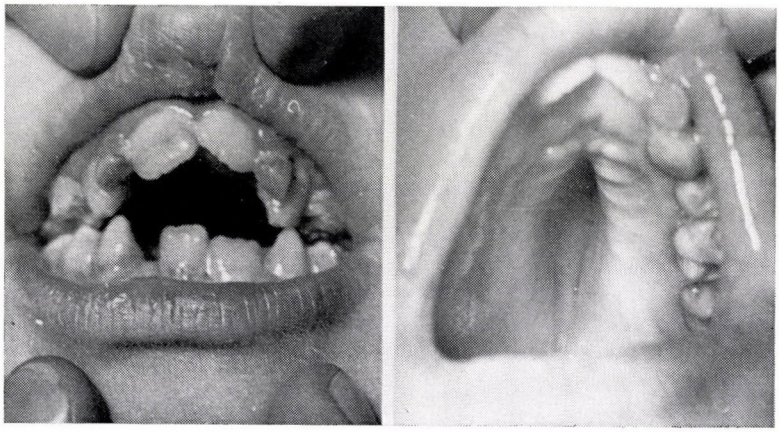

Fig. 7. Malocclusion and gothic palate

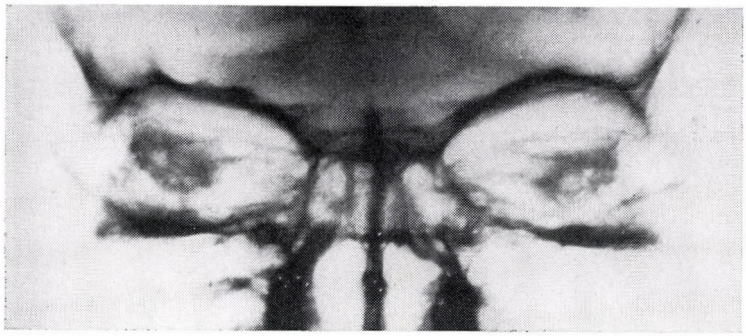

Fig. 8. Anteroposterior X-ray of the skull of a patient with mongolism

Chondral dysostosis affecting the skull may be regarded as a developmental anomaly of the praechordal and parachordal plates due to a weakened induction potential of the notochord. In mongolism, the cranium primordiale is not the only area of the skull showing changes: the splanchnocranium also reveals characteristic signs such as a hypoplasic maxilla, shortened vomer, and hypoplasic incisival bone. Combined, these retardations produce the gothic palate, cause malocclusion (Fig. 7) and bring forth the mongoloid orbit (Fig. 8) characterized by its most cranial point being the upper outer, instead of the upper inner, canthus.

This phenomenon is easily imitated in a simple model experiment. Two circles, corresponding to the orbits of the eyes, are drawn with India ink on a half-inflated rubber-balloon. As the balloon is further inflated so the circles grow symmetrically. Now if an inextensible thread has previously been fixed inside the balloon with one point of anchorage between and below the two circles and the other one just opposite it, then, on inflating the balloon, the circles will not grow symmetrically, but assume a "mongoloid" shape (Fig. 9).

With disturbed ossification of the primordiale cranium and retarded development of some of the bones of the splanchnocranium, mongolism is

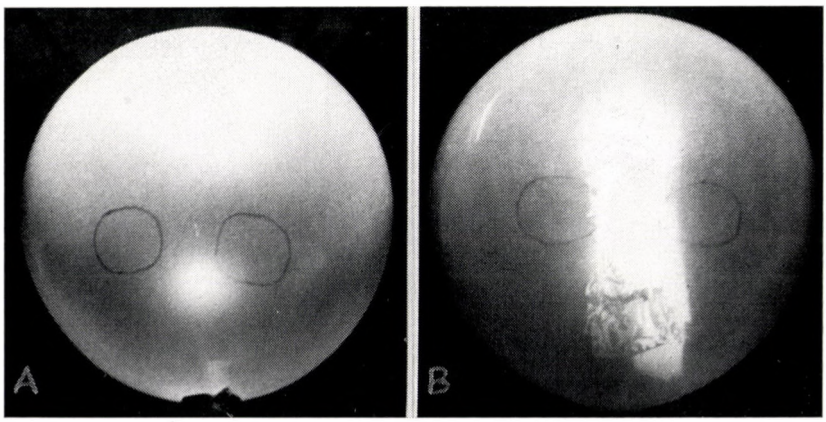

Fig. 9. Model experiment imitating skull development in mongolism (details above)

characterized by both chondral and desmoid dysostosis. Additional evidence of this is provided by the frequency of anomalous dentition and by BENDA's observations on the ossification of the cranial sutures and fontanels [11]. Skull formation and cerebral development are close correlates.

Since FRASER [22] had first described the child brain in mongolism, more than 25 papers have appeared discussing the neural lesions in this disease. On the whole, the brain of the child with mongolism shows immature tissues, hypoxia (hypervascularization, gliosis), and hypoplasia of the brain stem. For their degree these characteristic lesions depend on the age of the patient. They are the less severe, the younger the child was at death (1 to 3 years of age). In older patients the cerebral changes are more severe and varied, including many senile plaques, Alzheimer's neurofibrillar and neuronal degeneration (JERVIS, 23).

Pressure causes the nerve cells to atrophy and atrophy progresses with progressing pressure on the nervous system. By progressive pressure, progressing reduction in skull volume is meant here.

PRADER [24] distinguishes four phases of growth in extrauterine life:

(I) From birth to the third year of life the nervous system alone plays a part in growth.

(II) From the third year of life to the beginning of the period of puberty the synergistic effect of the STH, the thyroid gland, and insulin is responsible for growth.

(III) During the period of puberty the adrenal cortex and the gonads are the somatotrophic factors.

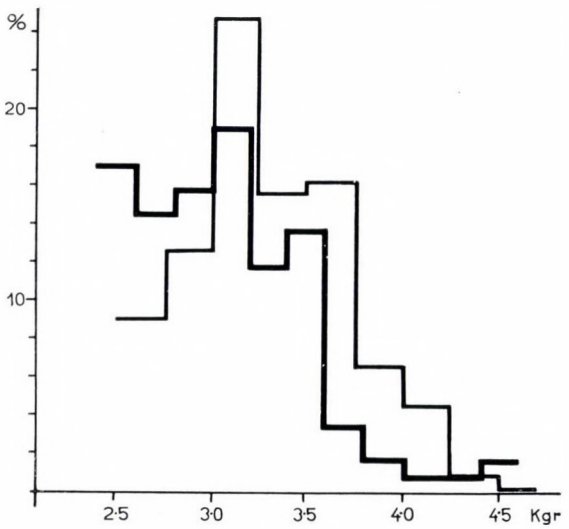

Fig. 10. Curve showing birth weight of 117 newborns with mongoloid (heavy line) and frequency curve of birth weights of the newborns in Hungary in 1959 (fine line). Had only the mongoloid children of more than 2500 g. birth weight been taken into account, the two curves would run the same course. As 20 per cent of the patients mongoloids are prematures, those of less than 2500 g weight at birth have been included. The identical frequency of the different weight groups is instructive

(IV) After the period of puberty growth appears to be due to the joint action of the androgenic hormone produced by the adrenal cortex and the hormones produced by the gonads.

Intrauterine somatotrophy is the same in patients with mongolism and in normal children (Fig. 10), but extrauterine growth in the former betrays distinct progressive retardation (Fig. 11).

This lagging rate of growth manifests itself chiefly after the third year of life, from which it is inferred that the nervous system has suffered no lesion that would adversely affect growth (Fig. 12).

The explanation for the somatic retardation is apparently to be sought in an inferior pituitary-thyroid-insulin synergism.

X-rays fail to throw light on pluriglandular insufficiency since in mongolism the sella is normal in size and shape. Clinical tests (reduced glucose tolerance; CSABAY, [25]) on the other hand, permit the conclusion that mongolism is concomitant to a diencephalic-hypothalamic lesion resulting from progres-

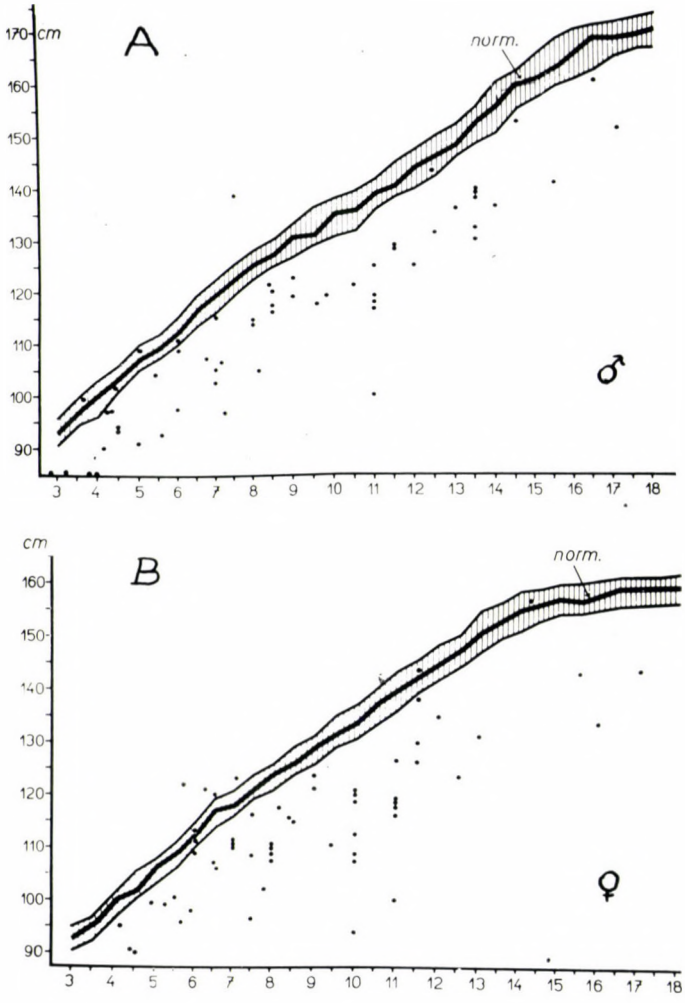

Fig. 11. Body length of mongoloid children. A: boys, B: girls

sive pressure on the brain. This is what makes it seem probable that a progressive reduction of the relative volume of the skull exerts a slow but gradually increasing pressure on both the cerebral cortex and the diencephalon, thereby producing a hypoxy-biotic condition. We assume that, primarily, this

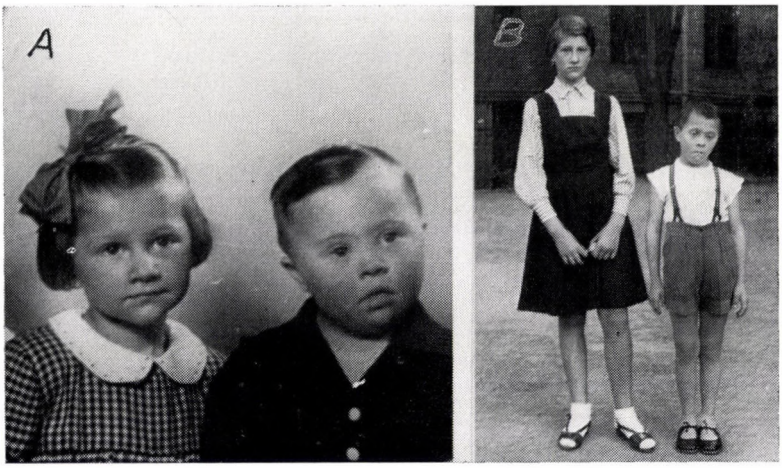

Fig. 12. A = Binovular twins 3 years of age, one of them suffering from mongolism. B = At the age of 13 years twin mongoloid is 35 cm less in height

condition interferes with the functional hierarchy of the diencephalon-pituitary-endocrine glands and, secondarily, acts upon the cortex starting there a process of progressive degeneration which ultimately results in oligophrenia and muscular hypotony.

Summary

Mongolism is a condition with an abnormal chromosome number at its basis and a peculiar type of mesenchymosis playing a part in its pathogenesis. This mesenchymosis interferes with the chondrogenic ossification of the face bones and the calvary and thereby gives rise to progressive microcephaly. This in turn exposes the nervous system to progressive pressure which assumedly results in a state of increasing hypoxybiosis.

This state may produce degenerative changes in the cerebral cortex and the diencephalon, occasionally even the cerebellum, and these may lead to oligophrenia, hypotony and a peculiar pluriglandular insufficiency.

REFERENCES

1. MITTWOCH, U.: (1952) The chromosome complement in a mongolian imbecile. Ann. Eugen. **17,** 37. — 2. JACOBS, P. A., BAIKIE, A. G., COURTBRAUN, W. M., STRONG, J. A.: (1959) The somatic chromosomes in Mongolism. Lancet, **1,** 710. — 3. FORD, C. E., JONES, K. W., MILLER, O. J., MITTWOCH, U., PENROSE, L. S., RIDLER, M., SHAPIRO, A.: (1959) The chromosomes in a patient showing both mongolian and Klinefelter syndrome. Lancet **1,** 709. — 4. LELONG, M.: (1949) Mongolien issu de mère mongolienne. Arch franç. Péd. **6,** 231. — 5. SAWYER, M. (1949) Case report: Reproduction in a Mongoloid. Amer. J. ment. Def. **3,** 204. — 6. SAWYER, M., SHAFTER, A. J.: (1957) Reproduction in a Mongoloid; a follow up. Amer. J. ment. Def. **6,** 793. — 7. REHN, A. T., THOMAS, E.: (1957) Family history of a mongoloid girl who bore a mongoloid child. Amer. J. ment. Def. **5,** 496. — 8. Editorial: (1954) Is Mongolism a metabolic error? Brit. med. J. **10,** 802. — 9. VAN DER SHEER (1914) cit. SZONDI, L.: A fogyatékos értelem. Egyetemi Nyomda, Budapest, 1925. — 10. DAVIDOFF, J. cit. INGALLS. — 11. BENDA, CL.: (1960) The Child with Mongolism. Grune & Stratton, New York. — 12. INGALLS, TH. H.: (1947) Pathogenesis of Mongolism. Amer. J. Dis. Child. **73,** 279. — 13. FATTOVICH, G.: (1957)

Contributo all' anatomia patologica dell' idiotia mongoloide. Cervello **33**, 241. — 14. HALFER, G.: (1957) Anatomia pathologica del Mongolismo. Relazione XXV. Congresso della Italiana Societa Pediatria. — 15. CLARA, M.: (1955) Entwicklungsgeschichte des Menschen. G. Thieme, Leipzig. — 16. TÖRŐ, I.: (1942) Az ember fejlődése. Egyetemi Nyomda, Debrecen. — 17. STOCKARD, A.: (1916) Die Entwicklung des Schädels. Beitr. path. Anat. **61**, 450. — 18. GREIG, J. cit. INGALLS. — 19. WOLBACH, R., BESSEY, J.: (1941) Vitamin A deficiency and the nervous system. Arch. Path. Chicago **32**, 689.— 20. WEATHERFORD, D. cit. INGALLS. — 21. GÖLLESZ, V.: (1960) In press. — 22. FRASER, J. (1879) cit. FATTOVICH. — 23. JERVIS, G. A.: (1948) Early senile dementia in Mongoloid idiocy. Amer. J. Psych. **105**, 102. — 24. PRADER, A. cit. LŐVEI: (1958) Gyermekgyógy. (Budapest) **12**, 361. — 25. CSABAY, L.: (1960) In press.

BEITRÄGE ZUR PATHOGENESE DER DOWNSCHEN KRANKHEIT

L. HORVÁTH

Die Downsche - Krankheit (Mongolismus) ist ein auf Chromosomenaberration beruhender Zustand, in dessen Pathogenese eine besondere Art von Mesenchymose eine Rolle spielt. Pathogenetisch erstreckt sich letztere auf die chondrogene Verknöcherungsstörung der Schädelbasis sowie auf die desmogene Verknöcherungsstörung des Gesichtsschädels und des Schädeldaches, auf welcher Grundlage Mikrozephalie entsteht. Dadurch wird das Nervensystem progressivem Druck ausgesetzt und auf dieser Basis dürfte ein fortschreitender hypoxybiotischer Zustand entstehen.

Dieser hypoxybiotische Zustand kann in der Hirnrinde sowie im Dienzephalon, aber auch im Kleinhirn degenerative Veränderungen hervorrufen, die die Entwicklung von Oligophrenie, Hypotonie und einer besonderen Art von pluriglandulärer Insuffizienz verursachen können.

ДАННЫЕ К ПАТОГЕНЕЗУ БОЛЕЗНИ ДАУНА

Л. Хорват

Монголизм (болезнь Дауна) является состоянием, обусловленным изменением числа хромозом, и в его патогенезе играет роль своеобразный мезенхимоз. Мезенхимоз патогенетически распространяется на хондрогенное расстройство окостенения основания черепа и на десмогенное расстройство окостенения лицевого черепа и черепного свода, и обусловливает прогрессирующую микроцефалию. В результате этого нервная система подвергается все усиливающемуся давлению, и этим, предположительно, вызывается повышающееся гипоксибиотическое состояние.

Гипоксибиотическое состояние может вызывать в коре головного мозга, а также в промежуточном мозге и мозжечке дегенеративные изменения, которые в свою очередь могут быть причиной развития олигофрении, гипотонии и своеобразной плюригландулярной недостаточности.

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