

GROWTH DISORDER OF THE SKULL IN MONGOLISM *

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Ever since human curiosity has made conjectures from the shape of the skull as to the function and activity of the brain hidden beneath its bony envelope, the relation between the brain and the skull has been a subject of great interest to science and philosophy. Phrenology and physiognomy, however, which flourished in the beginning of the last century, did not leave the uncertain ground of speculation until 1858, when Rudolph Virchow¹ made the first attempt to study the development of the skull by histological means. His famous work on cretinism, in which he explained the peculiar appearance of cretins as being due to an early ossification of the base of the skull, proved to be mistaken as far as cretinism is concerned, but his principal ideas about the importance of the synchondrosis speno-occipitalis and other sutures are generally accepted, and numerous reports have followed his work dealing with the development of the skull.

There are two conditions known which are associated with a marked shortening of the length of the base of the skull — chondrodysplasia and cretinism. My own studies have proved that there is a third entity, mongolism, which also is associated with a failure of the development of the skull in length. Chondrodysplasia and cretinism have attracted much interest and our knowledge of these maladies is fairly well established as far as the histological changes in the cartilage and the bones are concerned. The same is not true of mongolism in spite of the striking appearance of mongoloid children, to whom so much attention has been given since the first description of this malady 75 years ago. There are only a few publications dealing with the development of bone in mongolism, and no histological study of the development of the skull has been published to my knowledge. In 1924 Lauche²

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published a paper on mongolism and reviewed the few publications on this subject. He studied four metatarsals and ribs from mongoloid children aged 4, 10, 12 and 18 months, respectively. He mentioned the skull in 1 case but did not discuss the subject.

If we compare histologically the three disorders mentioned above, we may say that in chondrodysplasia growth of the base of the skull is arrested because of lack of development of the cartilage, which is absorbed early and replaced by ossified tissue. In cretinism growth of the bones of the skull is delayed because of lack of transformation of cartilage into bony tissue. The cartilaginous spaces in cretinism are open much longer than normally.

In mongolism the situation is much more complicated. X-ray studies by Siegert³ in 1910, and also our own x-ray observations, show that the appearance of centers of ossification in the carpal bones takes place early and that ossification comes to an early arrest. In a paper published recently⁴ the conclusion was drawn that the cartilaginous bones of the base of the skull show a lack of proliferation and irregularity in ossification. As a result the base of the skull remains proportionately smaller than normal and retains a formation present in the last months of embryonic development. Further development of the normal skull, consisting of growth and molding of the base, is interrupted and pneumatization is lacking. This was concluded because of the x-ray observation that the synchondrosis spheno-occipitalis, which is visible as a small cartilage disc in normal children during the first year of life, and sometimes even later, could not be noted in mongoloid patients after the first few months of life. Therefore, the cartilage may have been replaced by ossification. This assumption, however, is contradictory to the observations of Bean,⁵ who reported that the epiphyses of the bones are small and unite late, if at all. As a matter of fact, if the epiphyseal lines of the carpal bones in adult mongoloids are studied by x-ray, a line of almost microscopic thickness crossing transversely through the capita of the carpal bones is sometimes seen. This small line probably represents a remnant of cartilaginous tissue. Lauche observed that the cartilage does not become entirely absorbed and remnants of cartilaginous tissue remain unchanged for a long period of time.

By evaluating these facts, many of which appear contradictory,

the following problem was suggested. Does the cartilage become prematurely absorbed and replaced by ossified tissue, as occurs in chondrodysplasia, or does the cartilage remain unchanged, as in cretinism? What are the histological differences in these conditions? Such an investigation may decide some of the pending questions as to whether the growth disorder in mongolism is associated with an early or a premature ossification of the epiphyseal lines, or with a delay of ossification. If the latter be true, the problem arises as to whether the alterations in mongolism and cretinism are identical, which would suggest a thyroid disorder. If there is a difference in the histological appearance the question will be discussed whether or not this indicates an endocrine disorder and if so of what nature.

MATERIAL

Specimens of bones from 8 cases of mongolism were studied. These comprised the synchondrosis spheno-occipitalis from 6 cases, the synchondrosis spheno-ethmoidalis from 2 cases, and vertebrae from 2 cases.

In 1916 Stoccada⁶ published a paper on the synchondrosis spheno-occipitalis, its normal development, and the alterations occurring in cretinism. In this paper he described the synchondrosis at the time of birth, during the first decade, the second decade, and after further growth has ceased. My observations on control cases are in accordance with those of Stoccada. Therefore, it may be worth while to record a few points of interest concerning the development of the synchondrosis. The cartilage which lies between the occiput and the sphenoid bone does not form a simple disc at the time of birth but continues to develop toward the posterior clinoid process as a cartilage slide of the same size as the disc, forming the rostral dorsum of the clivus blumenbachii and the posterior clinoid process. The cartilage disc of the synchondrosis averages from 3 to 3.5 mm. in thickness. The cartilage cells form vertical columns in the center and are arranged in horizontal columns toward the occipital bone and the sphenoid body. Growth occurs in two directions. The cartilage disc grows in a vertical direction and the height of the disc increases steadily from about 7 mm. at birth to between 13 to 15 mm. at the age of 17 years. The horizontal cartilage columns proliferate

in the same manner as the epiphyseal lines of the long bones. The thickness of the cartilage disc is about 3 mm. and remains this size for almost the first 20 years of life. At about the age of 20 years the cartilage becomes gradually absorbed and disappears. According to Stoccada the area of proliferation measures between 200 and 300 μ and the area of ossification about 150 μ . The appearance is identical with that seen in the ribs and the epiphyseal lines of the long bones. It may be mentioned that the cartilage proliferation appears slightly more active toward the occiput than toward the sphenoid. After the first year the cartilage frequently shows a tongue-like protrusion into the sphenoid body. Therefore, the synchondrosis appears F shaped. This cartilage tongue was found regularly in our material.

Case 1: A mongoloid male (38-15) aged 7 months and 10 days. The synchondrosis measures 1.5 mm. in thickness and 7 mm. in height (Fig. 1). The cartilage shows small embryonic cells and no preparatory columns are visible. Many small primary marrow cavities are visible without immediate communication with the cartilage areolae. The central medullary cavity is enlarged and touches the cartilage on a broad section by a few, thick, osseous trabeculae. The edge is heavily ossified (see Fig. 3).

By comparison with the measurements of a normal synchondrosis (by Stoccada⁶) the height of the synchondrosis corresponds to the normal, but the width of 1.5 mm., instead of 3 to 4 mm., is much smaller than would be expected. The ossification is obviously abnormal, the growth arrested, the cartilage does not show preparatory involution, and the bony tissue is much more heavily ossified than is seen normally at this age.

Case 2: A mongoloid male (38-25) aged 8 years and 8 months. The synchondrosis is distinctly visible as an F shaped tissue disc between the occipital and the sphenoid bone (Fig. 2). The width of the cartilage is 1.2 mm. A cartilage tongue 1 mm. in length protrudes into the sphenoid bone. The cartilage of the clivus toward the posterior clinoid process is visible and measures 300 μ in thickness. The height of the cartilage disc measures 6 mm. Microscopically small cells are visible in the center of the cartilage running in a vertical direction. Toward the border of the bone on each side the cartilaginous cells are arranged in a horizontal direction. The length of the preparatory zone measures 150 μ .

The capsules contain two or four (no more than six) rather small cells, ovoid in shape. None of these capsules is in direct contact with the medullary cavities; they are closed and entirely embedded in cartilaginous tissue. The border toward the bone is penetrated by numerous, small round cavities containing bone marrow. These cavities are surrounded by cartilage and only a few communicate with the central medullary cavity of the sphenoid body. The rather even cartilage border shows calcification. There are many ossified ridges running in a horizontal direction. Vertical ridges in places separate a second layer of medullary cavities from the central cavity. These cavities are surrounded by heavily ossified tissue and are without communication with other cavities.

Histologically the synchondrosis is much smaller than is seen normally. Growth in the cartilage is arrested. There is heavy ossification of the bone with formation of primary and secondary ridges of bone.

Case 3: A mongoloid female (38-17) aged 9 years and 8 months. The cartilage measures 4 mm. in thickness and 10 mm. in height. It appears to be artificially swollen and its natural width was probably less. The clivus cartilage has entirely disappeared. The cartilaginous synchondrosis fails to show a regular arrangement of the cells and only near the borderline are a few short columns of cartilage cells visible. None of these contains more than two to four small cells. The capsules are without communication with the bone marrow. The cartilage edge is perforated by small marrow cavities which are entirely framed with heavily ossified ridges. The borderline is heavily calcified and thick ridges of bone divide the central marrow cavity connected by transverse ridges which separate smaller marrow cavities (Fig. 4).

The growth in this case appears to be entirely arrested.

Case 4: A mongoloid male (38-32) aged 14 years and 11 months. The cartilage border of the synchondrosis is straight, lacking preparatory cartilage cells. A few, empty, small primary cavities are visible. The edge of the cartilage is heavily ossified. Although this boy was almost 15 years of age, the posterior clinoid process is still entirely cartilaginous. The sphenoid body shows ossified spongiosa, the spaces are filled with bone marrow and the ridges are definitely ossified. No sphenoid sinus has developed.

Histologically this case differs from those described above. The

heavily ossified cartilage border is rather straight. There is only one large central marrow cavity with few ridges of bone and no smaller secondary marrow cavities. The appearance is suggestive of cretinism.

Case 5: A mongoloid male (38-22) aged 20 years and 6 months. The upper part of the synchondrosis is entirely absorbed and replaced by bony marrow. In the lower part is a broad cartilaginous remnant 1.8 mm. in length left which is perforated by a larger medullary cavity. This cavity contains bone marrow. The edges of the cavity are calcified on one side and cartilaginous on the other. The cartilaginous remnant appears to be homogeneous and the small cells do not reveal any direction in arrangement. The edge is even and covered with a thin calcified crust; no signs of further transformation of cartilage into bone are visible. Both tissues are resting. The sphenoid body shows no sinus formation.

Case 6: A mongoloid male (37-8) aged 30 years. In this case no synchondrosis speno-occipitalis is visible. The sphenoid body is small and shows no sinus formation. In one area a small cartilaginous remnant is visible which was probably left from the cartilage usually separating the anterior and posterior part of the sphenoid body during the first years of life.

Cases 5 and 6 show that the beginning of the resorption of the cartilage spaces occurs within the normal period. The cartilage becomes resorbed without showing signs of activity, the resorption being slow and incomplete.

THE SYNCHONDROSIS SPENO-ETHMOIDALIS

The synchondrosis speno-ethmoidalis, in contrast to the synchondrosis speno-occipitalis, consists of fibrous tissue. It undergoes ossification according to the process which unites the sutures of the skull and ossifies the membranous bones. Figure 7 shows the synchondrosis speno-ethmoidalis in a mongoloid boy 9 years and 8 months old. The anterior clinoid processes are rather far apart from the dorsum sellae and no ossification is taking place. Only the edges of the synchondrosis and of the anterior clinoid process are heavily ossified. It is of interest that this synchondrosis forms a fibrous tongue protruding into the sphenoid body. In another specimen from a 15 year old mongoloid child the

synchondrosis speno-ethmoidalis was also wide apart without signs of ossification. This fact is of interest because Timme⁷ described the shape of the sella turcica in mongolism and noticed a peculiar appearance of the anterior part of the sella by x-ray examination. The same observation was later recorded by Tumpeer.⁸ Timme interpreted this change to be the result of enlargement of the pituitary gland. Microscopic examination, however, shows that the radiographical appearance is due to the wide open synchondrosis and that the shape of the sella is independent of the size of the pituitary gland in mongolism. Moreover, the appearance of the sella turcica in mongolism corresponds to the x-ray appearance of a full term embryo in which the sella turcica also is separated into two sections.

THE VERTEBRAL COLUMN

Figures 5 and 6 show ossification of the cartilage centers of the vertebral bodies. The cartilage of a 2 day old mongoloid child (Fig. 5) shows a normal appearance of the cartilaginous border. There are many preparatory columns present and the ossification appears active. Another specimen from a 2 months old mongoloid infant shows complete degeneration of the cartilage columns. The cartilaginous border is ossified and several primary marrow cavities are recognizable. On the side of the bone tissue there was a huge ridge of bone visible which is parallel in direction with the cartilage border and separates smaller marrow cavities from the central cavity (Fig. 6).

These observations are of interest because in Figure 5, 2 days after birth, the original arrangement of bone and cartilage still appears to be normal. Figure 6, from a mongoloid child 3 months after birth (1 month premature), shows complete degeneration of the cartilage and abnormal bone formation similar to the transverse ridges of bone found in the synchondrosis speno-occipitalis.

THE RIBS

Figure 8 shows the cartilaginous border of a rib from an 8 months old mongoloid child. There are only a few, rather short, preparatory cartilage columns visible. The growth is obviously arrested. However, the histological appearance of the rib cartilage in mongolism is by no means specific. Although there may be a

temporary arrest of growth a comparison of specimens at different ages shows that the ribs grow according to the height of the child. Measurements carried out by Davenport⁹ show that the circumference of the thorax in mongoloid children is comparatively normal. The rib, therefore, is not a suitable subject for study of the growth disorder in mongolism and there is no need to discuss at length the observations reported in the literature.

DISCUSSION

The recorded observations settle definitely the question whether or not mongolism is associated with premature ossification and closure of the epiphyseal lines. Histological studies have proved that such premature ossification does not take place. There is no relation whatsoever to chondrodysplasia. Histologically chondrodysplasia and mongolism differ definitely.

The reports on the mongoloid epiphyseal lines are also of interest in relation to the problem of hyperthyroidism studied by Clark,¹⁰ who considered mongolism as a "fetal hyperthyroidism ceasing at birth," an idea recently reiterated by Meyers.¹¹ This problem was discussed at length in a paper dealing with the thyroid in mongolism.¹²

In contrast to hypothyroidism, in which ossification is delayed, most authors are of the opinion that hyperthyroidism produces premature differentiation and ossification preceded by a period of stimulation of growth. The obvious retardation of growth in mongolism rules out such an interpretation. Smith and McLean,¹³ who recently studied the effect of hyperthyroidism on the growth and the chemical composition of bone in rats, demonstrated that toxic hyperthyroidism may lead eventually to premature cessation or retardation of growth, but this effect is due to toxemia and follows an increase in weight and in substance of bone. In mongolism the bones are small and underweight and no period of increased growth is recognizable. The alterations are associated with the persistence of the skull sutures and the epiphyseal lines of the long bones, which rules out hyperthyroidism.

The question whether or not mongolism is due to a thyroid deficiency and therefore identical with the growth disorder in cretinism is of importance. The growth disorder due to hypothyroidism is well known and is beyond the limits of this paper to

discuss at length. However, a few facts which indicate that the disorder in mongolism is distinctly different from that of cretinism may be summarized as follows:

(1) X-ray observations in cretinism indicate that the appearance of bone centers is delayed and the cartilage spaces remain wide open for a long period of time, even if the normal period of growth has ceased. X-ray observations in mongolism indicate that the appearance of bone centers is normal, but that growth of the bones is minute. Therefore the carpal centers, for instance, remain much smaller than in normal children. In mongolism the cartilage spaces are extremely small, being easily overlooked. A junction of the epiphyseal lines occurs prematurely but some cartilage remnants remain without being absorbed.

(2) From an anatomical point of view the vault in cretinism is always large, the skull being normal or even above normal in circumference while the base of the skull remains small. In mongolism the whole skull is undersized and the circumference, after the first half year of life, is definitely below normal. In mongolism the fontanelles remain open for a rather long period of time. Sutures do not close at the normal time.

(3) From a biological point of view cretinism is definitely associated with high cholesterol values and a low metabolism. In mongolism the cholesterol values are normal and the metabolic rates also.¹⁴

(4) Although the histological appearance of the cartilage in cretinism and mongolism appears to be somewhat similar at first sight, there are marked differences if observed in more detail. In cretinism the cartilaginous border of bone forms a straight line with few or no primary medullary cavities. The ridge of ossification is rather thin. The preparatory columns show a normal appearance; the cartilage, however, degenerates where lack of thyroid is not corrected by therapy or experimentally produced by complete thyroidectomy. According to Stoccada, this is easily recognizable; the marrow cavities are rare, irregular in shape, and separated from the cartilage by a ridge of bone. The disorder of ossification causes a persistence of cartilage. Siegert³ and Stoccada⁶ interpreted the lack of ossification as being due to a deficiency of the bone marrow which is not able to absorb the cartilage and to stimulate sufficient growth. In mongolism the

histological appearance is usually different, although at times the condition may be confused by a secondary thyroid deficiency (see Case 4). The ossification is active and calcification of the spongiosa is not delayed. There are a number of medullary cavities. The border of the bone is arcade shaped. Lack of proliferation of cartilage is easily recognizable. The cartilage discs are extremely small and proliferation and formation of preparatory columns are arrested.

These observations are in accord with Lauche's studies of metatarsal bones.² His Cases 1 and 4, mongoloid children aged 4 and 18 months respectively, showed a complete lack of cartilaginous proliferation. The cartilage was found to be covered with a more or less thick ridge of bony tissue which separated the cartilage from enlarged marrow cavities. In Cases 2 and 3, children 10 and 12 months old respectively, slight traces of cartilaginous proliferation were still recognizable. The bony tissue formed transverse ridges parallel to the cartilage border, which caused the formation of small secondary marrow spaces. Lauche pointed out that in normal children growth goes on during the ossification period, except in the ribs, as long as cartilage is available for ossification. In mongolism this growth is arrested, although enough cartilaginous tissue is still available. In 1902 Kassowitz¹⁵ reported that the marrow spaces were not finger-like processes, but occurred in the form of rounded, knob-like projections into the zone of cell columns, and that consequently the spongy bone did not consist of long tracts of bone, but instead of rounded cavities.

The few studies of the growth of bone in mongolism, some of which seem to be contradictory, are rather well in accord if the same bone structure is concerned. The distal and not the proximal epiphyseal lines are noteworthy. Moreover, one has to bear in mind that growth in mongolism is somewhat irregular and periods of retardation may be followed by periods of more active growth.

The facts gathered above, especially the normal appearance of the centers of ossification but delay of further growth, the small size of the cartilage discs, and the general growth disorder involving not only the cartilaginous epiphyseal lines but the membranous bones of the skull, indicate that the growth disorder is definitely different from that of cretinism. If the arrest of

growth were restricted to the skull, the simplest explanation would be that the lack of development of the brain is the cause of the lack of further development of the skull. Such an explanation is correct for many forms of microcephaly in which the growth of the brain is arrested while the growth of the body continues undisturbed. Although it is true that many microcephalic patients remain dwarfs and that general endocrine deficiency is frequently associated with microcephaly, the arrest of growth of the brain and of the skull precedes the arrest of the growth of the body for many years. Microcephalic patients show a striking disproportion between circumference of the skull and the rest of the body, and observations prove that these patients grow at a normal rate during the first years of life while the skull remains undersized. Not until several years of life have passed does the growth disorder of the body become apparent in microcephaly. The fact, however, that in later life microcephaly is frequently associated with a general endocrine disorder indicates an influence on the part of the brain on the endocrine glands. In mongolism measurements and studies of the brain development indicate that during the first half year of life the weight of the brain corresponds to normal, while at the same time a general growth disorder of the skull and the long bones is recognizable. The arrest of differentiation and the absence of growth stimulation apparently parallel the arrest of further development of the brain but do not depend on it. Moreover, the alterations of the vertebrae and of the long bones are independent of the brain and develop at the same time arrest of growth of the skull occurs.

COMMENT

By evaluating all factors at hand there is a strong indication that the growth disorder in mongolism is due to the absence of agents which induce differentiation and growth. It is generally assumed that these factors are related in some way to the pituitary gland. Lauche expressed the opinion that the growth disorder in mongolism is the reverse of acromegaly. Studies of the pituitary gland led me also to the conclusion that an insufficiency of the anterior lobe is responsible for the postnatal growth disorder in mongolism.

Erdheim,¹⁶ who studied the growth disorder of the cartilage in

acromegaly, emphasized that in this condition proliferation of cartilage is renewed if cartilage remnants are available (ribs and long bones of young adults). If the cartilage in the epiphyseal lines has disappeared further proliferation is impossible, but the cartilage of the joints shows activity which eventually leads to degeneration. Erdheim is of the opinion that a renewal of cartilage activity is one of the main factors in the acromegalic disorder. On the other hand, hypofunction of the pituitary gland inhibits enchondral ossification and the epiphyseal lines remain open. Erdheim¹⁷ earlier had stressed the fact that the Paltauf dwarf is astonishingly small because the proliferation of cartilage in the epiphyseal lines is completely arrested or markedly diminished through hypofunction of the pituitary. The epiphyseal lines remain open and enchondral ossification is completely or almost completely arrested. The assumption expressed by earlier writers that the cause of dwarfism is a premature ossification of the epiphyseal lines is therefore incorrect, according to Erdheim.

Recent experiments, however, may modify the conclusions drawn by Erdheim. We have to bear in mind that in animals, in whom the epiphyseal cartilage usually disappears, this cartilage will persist if the animals are castrated (McLean *). It is possible, therefore, that the persistence of cartilage in dwarfs and mongoloids is not due to a direct dysfunction but to a hypoplasia of the gonads which is almost always associated with pituitary dysfunction.

Of even more importance in regard to the relation between growth disorders of bone, especially of the skull and pituitary dysfunction, is the work of Mortimer.¹⁸ He studied the effect of hypophysectomy on young rats and his results may be quoted briefly as follows:

“Comparing the measurements of the hypophysectomized and the control, it appears that the greatest disturbance of growth in the hypophysectomized animal’s cranium is in the anteroposterior direction, both cranial height and width showing no failure in growth. Occipito-nasal length is 16.1 per cent less and fronto-occipital length is 11.4 per cent less than the control, but the chief defect is in the nasal bones, which are almost a quarter less long than normal. . . . Even more marked is the resultant defect on

* Personal communication.

the lower incisor and mandible, as shown by 34 per cent retardation in the lower incisor and a 43 per cent in the body of the jaw. . . . Absence of the anterior lobe of the pituitary imposes a handicap on growing bone in general which tends, peculiarly and particularly, to affect the growing snout, owing to the cancellous type of bone of which it is largely composed, the brain-case being structurally of more compact bone, which, while undoubtedly affected by hypophysectomy, is so to a less degree."

"The frontal bone is similarly affected in the areas between the vascular expansions, which suffer to a marked degree. This is particularly true in the anterior expansion which occupies the site more closely homologous to the human frontal sinus. It is not only much shorter anteroposteriorly (two-thirds the length), but is also much less in its vertical measurement, while its outer table, instead of forming the convexity of the fronto-nasal angle is depressed and somewhat concave, and its contained marrow aplastic." "A similar condition is present in the basal bones of the skull which are considerably less 'expanded' than normal, and in length are 20 per cent shorter than in the control. The ethmoid and its cribriform plate, as well as the zygoma are considerably smaller."

Mortimer discussed the question that "a possible explanation suggests itself in that growth of the brain-case as a whole is undoubtedly dependent upon growth of the brain; in the hypophysectomized animal the brain is not so large as in the control and can be accommodated adequately in a brain-case which is 11.4 per cent shorter than normal and whose height and width are normal."

It is obvious that the postnatal growth disorder in mongolism is somewhat similar to the effect of hypophysectomy in rats. The mongoloid deficiency is marked by delay in growth in length of the base of the skull, lack of development of the masticatory apparatus, lack of sinus development and pneumatization of the skull, shortness of the nose with depressed bridge, and fetal proportion between brain case and face.^{4, 19, 20}

From these observations it is to be concluded that the postnatal development of the mongoloid child is characterized by a marked deficiency of pituitary action. Since the pituitary insufficiency is less pronounced in later life,^{19, 21} and the absence of the growth-stimulating hormones is most marked immediately

after birth, the assumption seems to be justified that at the time of birth the pituitary of the mongoloid individual has not reached the normal stage of development which enables the gland to take over the functions imposed upon it by extra-uterine life.

All these data refer to the postnatal development. Mongolism, however, is present at birth and it is still a subject of controversy as to whether the pituitary has much, if any, influence upon the prenatal period of growth. According to Collip,²² "in early stages of ontogenetic development the organism must have an extra-hypophyseal source of growth-stimulation substances." Mongolism is, apparently, due to a deficiency of the agents that stimulate differentiation and growth during the prenatal and postnatal stages of development.

SUMMARY AND CONCLUSIONS

1. A histological study of the synchondrosis speno-occipitalis, of the synchondrosis speno-ethmoidalis, and of tissue from the vertebrae in mongolism is presented.
2. It is shown that proliferation of the cartilage is absent or insufficient. The histological differences between mongolism, chondrodysplasia and cretinism are demonstrated and discussed.
3. The growth disorder in mongolism is not restricted to the cartilaginous epiphyseal lines but involves also the membranous bones.
4. An analysis of the observations indicates that the development of the growth disorder known as mongoloid deficiency appears to be dependent on a congenital absence or deficiency of those agents which, either from hypophyseal or extrahypophyseal sources, stimulate differentiation and growth.

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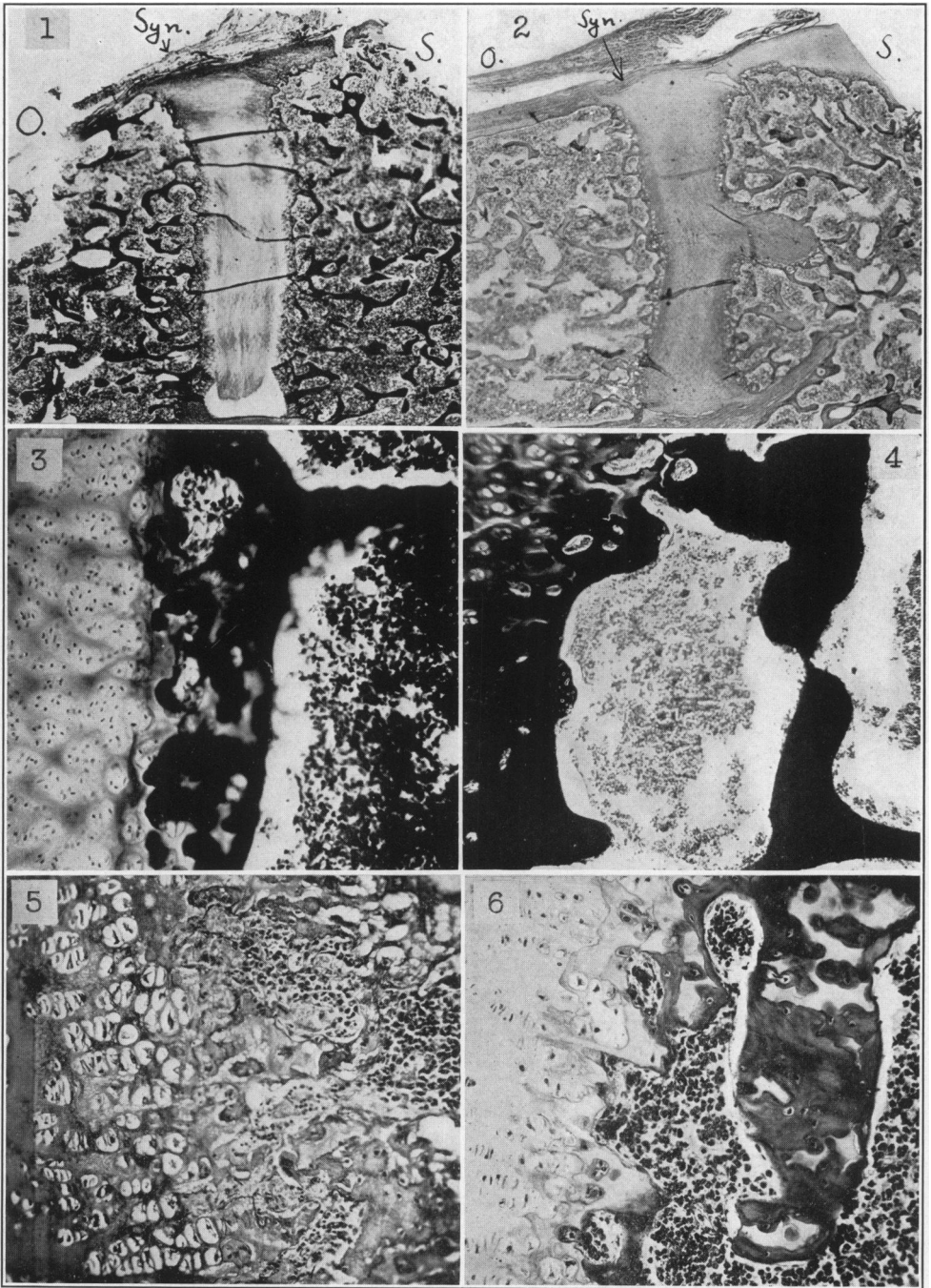
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DESCRIPTION OF PLATES

PLATE 32

- FIG. 1. Synchondrosis speno-occipitalis (Syn) in a 7 months old mongoloid boy. Width 1.5 mm., height 7 mm. S = sella turcica (posterior clinoid process removed with hypophysis); O = occipital part of clivus. Gross appearance normal. $\times 8$.
- FIG. 2. Synchondrosis speno-occipitalis (Syn) in an 8 year and 8 months old mongoloid boy. Width 1.2 mm., height 6 mm. The disc is shorter and smaller than normal. S = sella turcica (posterior clinoid process removed with hypophysis); O = occipital part of clivus. Note the cartilage slide forming the dorsum of the sella turcica and the posterior clinoid process. $\times 8$.
- FIG. 3. Same as Figure 1. Note the absence of preparatory cartilage columns. Many small primary medullary cavities are seen. The cartilage edge is heavily calcified. Note the large central medullary cavity. $\times 110$.
- FIG. 4. Cartilage border of synchondrosis speno-occipitalis in a 9 year and 8 months old mongoloid girl. Note the absence of cartilaginous preparatory columns. Many primary medullary cavities are present. The edge is heavily ossified. Note the formation of transverse ridges of bone. $\times 110$.
- FIG. 5. Vertebra from a 2 day old mongoloid baby (body 40 cm. in length). The cartilage shows normal preparatory cell columns. The bone marrow is active with slight irregularities but still within normal limits. $\times 110$.
- FIG. 6. Vertebra from a 3 months old (born 1 month prematurely) mongoloid baby (length 52 cm.). Note the complete arrest of cartilage growth. The bone forms transverse ridges, parallel to the cartilaginous border. $\times 110$.



Benda

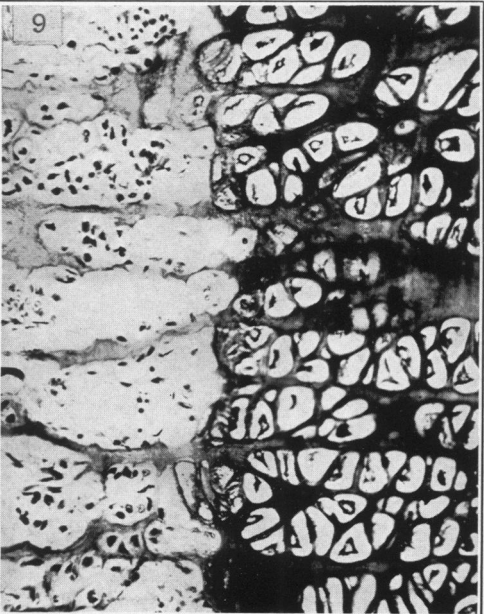
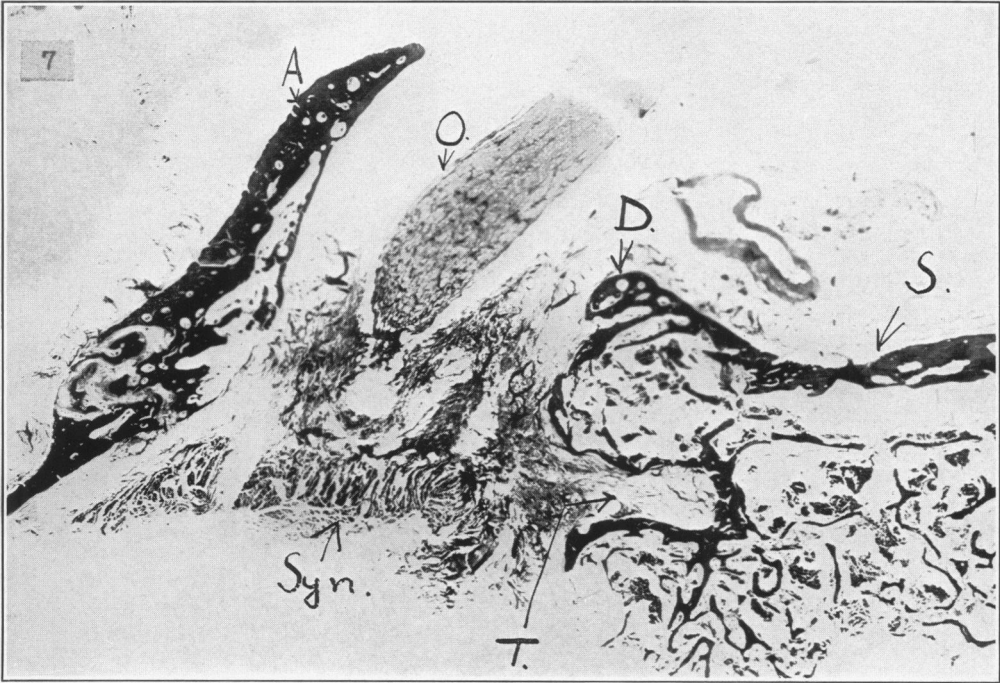
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PLATE 33

FIG. 7. Synchondrosis speno-ethmoidalis from a 9 year and 8 months old mongoloid girl. A = anterior clinoid process; O = optic nerve; D = dorsum sellae; S = sella turcica; Syn. = synchondrosis of fibrous tissue. The synchondrosis is wide open. T = fibrous tongue protruding into the sphenoid body. $\times 10$.

FIG. 8. Cartilage from the rib of an 8 months old mongoloid child. Note the complete arrest of cartilaginous proliferation. The bone appears normal. $\times 220$.

FIG. 9. Cartilage from a normal rib from a control case of the same age. The magnification is identical. Note the large cartilaginous cell columns.



Benda

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