CHONDRODYSTROPHIA FOETALIS

IN THE FOETUS AND THE INFANT.

Thesis submitted for the Degree of M.D. to the

University of Edinburgh

By

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INTRODUCTION.

In writing about the condition generally known as Achondroplasia, one feels that an apology is due for the very fact that an attempt should be made to swell the gigantic number of publications on the subject. This holds all the more because recently the disease has been so admirably discussed by Dr. Murk Jansen(1) of the University of Leiden, whose monograph has elicited an answer from Professor Arthur Keith(2), written in the way we are accustomed to in his works.

Comparatively common though that form of chondrodystrophia foetalis is which is generally designated as achondroplasia and which corresponds more or less to Kaufmann's(3) hypoplastic type, the variety that author called hyperplastic seems to be much rarer and Jansen actually doubts its existence. As it was my good fortune to observe a case and procure a series of skiagrams of the skeleton, I make it my excuse for choosing this subject for a Thesis.

All the cases came under observation at the Infirmary for Children, Myrtle Street, Liverpool, and my thanks are due to Drs. P. Davidson and N.P. Marsh, Honorary Physicians and Mr. R.C. Dun, Hon. Surgeon for

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(1) Dr.Murk Jansen. "Achondroplasia". Bibl.No.88
(2) Prof.Arthur Keith. Abnormal Crania,etc. Bibl. No.94
(3) Ed.Kaufmann. Untersuchungen ueber die sogennante foetale Rachitis. Bibl. No.43.

their permission to make use of the notes, to Dr. C. Thurstan Holland, Hon. Medical Officer to the X-ray department, for his kindness in helping me to interpret the skiagrams and his permission to publish them, and to Miss E. Fairclough, assistant to the Electrical Department for the readiness with which she has put her skill and time at my disposal for procuring the skiagrams and photographs.

I have drawn freely on the writings of the authorities on the subject and have acknowledged my indebtedness, wherever possible, in the text. A somewhat fuller account of the literature is given in the Bibliography at the end which has been arranged in chronological order and numbered. These numbers are referred to in the foot-notes.

Historical.

There is no doubt that a condition of dwarfism in adults, with definite facial characters, short limbs, a well developed trunk and a large head, with normal intellects, in many cases, however, accompanied by certain psychical peculiarities, in short, of what we now call an achondroplastic type, was known in the very oldest days of which we have any record.

A complete review is given of dwarfs mentioned in history, with the genealogy of many of them, in the chapter on Dwarfism by H. Rischbieth in The Treasury of Human Inheritance(1) with references ranging from the Old Testament (Lev. Ch.XXI. V.16-20) to recent works. Some of these were undoubtedly achondroplasts and many interesting points can be found in those records.

One is, that it has always been recognised that the sexual appetite was excessive in those cases and the Egyptian deity Bes, supposed to be the god of sexual intercourse, was given a shape very suggestive of achondroplasia, while the panther's spots and panther's tail, which are shown in some of the figures, are said to be indicative of the animal qualities attributed to the prototype of Bes.(2)

Domitian's dwarf gladiators are said to have been

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(1) Treasury of Human Inheritance. Bibl. 89.
(2) Compare frontispiece to Jansen's "Achondroplasia" l.c. and Prof.G.Elliot Smith's introduction to that work.

achondroplasts and a caricature statuette of the Emperor Caracalla shows the characteristic features of the disease.

Later Atila was described in a way suggestive of the condition while more recent and better authenticated instances are too numerous to mention.

On the other hand, in the 18th century, cases were described as congenital rickets in babies, which were, most likely, examples of achondroplasia(1). Since then a great number of records have been published as instances of "foetal rickets" by different observers(2). Later workers take care to designate those cases as "so-called" foetal rickets(3).

There can be little doubt that a great many different bone-conditions were included in these descriptions and great confusion existed as to the actual nature of this mysterious affection. This was rendered worse by the fact that no less an authority than Virchow(4) described a case in 1856, as that of a "newly-born cretin" which seems to have had all the features of the common form of chondrodystrophia.

At that time and for many years to follow the connection between the foetus suffering from congenital rickets and the adult dwarfs mentioned above was not

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(1) Klein. Rachitis congenita.etc. Bibl.1.
(2) Vide Bibl.2-7,9,10 and 12.
(3) Müller. Ueber die sogenannte foetale Rachitis. Bibl.15.
(4) Virchow. Ueber d.verbreitung d.Cretinismus.etc. Bibl.11.

understood although the micromelic element in the foetal deformities had drawn the attention of several observers[1]

In 1876, however, Parrot[2] described a condition to which he gave the name of achondroplasia and which he differentiated from other forms of congenital osseous lesions. Later[3] he described the case of a boy, aged 7½ years, whose body length was 93 c.m. and who was distinguished by adiposity, shortness of limbs, especially the lower ones, a depression of the bridge of the nose and irregularities of dentition. The mental capacity was only slightly impaired.

Kirchberg and Marchand[4] coined the name micromelia chondromalacica for the foetal condition.

In 1892 Kaufmann[5] gave the result of careful and exhaustive investigation of thirteen cases in the dead-born foetus and definitely broke with the conception that cretinism or rickets and the disease under discussion have any connection. He used the term chondrodystrophia foetalis for those forms of congenital bone disease which were best known as achondroplasia but, by distinguishing different varieties, he is able to include cases which are in many respects totally unlike the

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(1) Winkler. Ein Fall von foetaler Rachitis mit Mikromelie. Bibl.16.
(2). Parrot. Les lesions osseuses, etc. Bibl.22.
(3) Parrot. Sur les malformations achondroplasiques, etc. Bibl.22.
(4) Kirchberg & Marchand. Ueber die sogenannte foetale Rachitis. etc. Bibl.39.
(5) Kaufmann. loc.cit.

fat, micromelic cases which even now are usually described by the name invented by Parrot.

Classification of Foetal Bone-Diseases.

To avoid confusion when discussing a certain type of congenital bone lesions a good classification is highly desirable. One cannot, however, get away from the feeling that, even now, our knowledge of the subject has not a basis solid enough to build a satisfactory classification on.

Dr. Ballantyne(1) in his Manual of ante-natal Pathology gives as a desideratum the grouping of the foetal bone-diseases "in classes according to the period in ante-natal life when they were developed". A step in that direction has been made by Jansen(2) who fixes on the period of between the 4th and 8th week of embryonic life as that in which the morbid influences act which cause the achondroplastic deformities. Whether this is justifiable assumption will be discussed later. If, as he claims, the morbid process is one and the same in most of the varieties of congenital skeletal defects, the classification suggested in Dr. Ballantyne's work would be the ideal one. But we must learn a great deal more about the etiology of the various forms before that ideal

(1) Ballantyne. Manual of ante-natal Pathology. Bibl.64.
(2) Bibl.88. loc.cit.

can become a reality. When we come to discuss what is known about the causative factors we shall compare the different views concerning them.

If we exclude simple and localized deformities as absence of individual bones or parts of them, premature closure of one or more sutures (although these latter seem to be on the border line), those due to amniotic adhesions, etc. amd confine ourselves to those conditions which appear to attack chiefly a certain type of pre-osseous tissue, the method usually adopted, amongst others in Cautley's[1] text-book on Diseases of Infants and Children, seems convenient for practical purposes. It must be remembered, however, that recent investigations on bone formation threaten to upset all our present views on this subject and the following classification is only adopted because of its practical advantages and may prove altogether untenable when we know more about th the process of osteo-genesis.

I. Cases with changes in bone developed in cartilage.

II. " " " " " " membrane.

III. " " defect in bone derived from the periosteum (2).

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(1) Cautley. Diseases of Infants & Children. Bibl.85.

(2) It is chiefly the periosteal bone formation which is being discussed, in fact the occurrence of which is actually denied by the most recent investigators, on apparently good grounds. We shall refer to this later. It serves to demonstrate on what dangerous ground we are treading when attempting any classification at all.

Group I. is the one with which we are concerned here Kaufmann subdivided it into -

a. Chondrodystrophia foetalis hypoplastica.

b. " " hyperplastica.

c. " " malacica.

The latter variety can hardly be considered a definite subdivision as softening of the cartilages with some mucoid changes may be present in both a. and b. and only these two can really be distinguished.

The only pure example of Group II. is cleido-cranial dysostosis which we shall have to contrast later with Group I.

Group III. has generally been known as Osteogenesis imperfecta but this name might with advantage be used to denote the whole subject of congenital defect of bone. Synonyms or varieties, we are hardly in a position to judge which, are:- infantile osteo-malacia, osteo-psathyrosis, fragilitas ossium, etc. It is altogether outside the scope of this thesis.

CHONDRODYSTROPHIA HYPOPLASTICA.

I propose to give a short description of the classical type of the disease in the foetus and young child.

The baby achondroplast has a very striking appearance and the accompanying photograph (Plate I.) of Dorothy P. aet. 18 months at the time, will give a better idea of the distinguishing features than any word picture could. She is the fifth child of healthy parents in whose family history on neither side do any known instances of deformity occur. At the end of her fourth pregnancy the mother gave birth to a well-developed but still-born child at full time. One sister died of acute broncho-pneumonia when 2 years old. The other children are alive and healthy. The child was breast-fed up till the age of 10 months and is now getting a suitable diet of cow's milk, milk pudding, etc. Her health from birth has been good and the reason why she was brought to the Out-Patient Department was that her mother had noticed that "baby's back was not quite straight". The appearance had never struck anyone as being different from that of other babies, except that she looked "stronger".

The child shows all the characteristics of achondroplasia. The rounded kyphosis of the lower dorsal and upper lumbar regions, found in all cases, was rather more marked than usual and the antero-posterior movements of

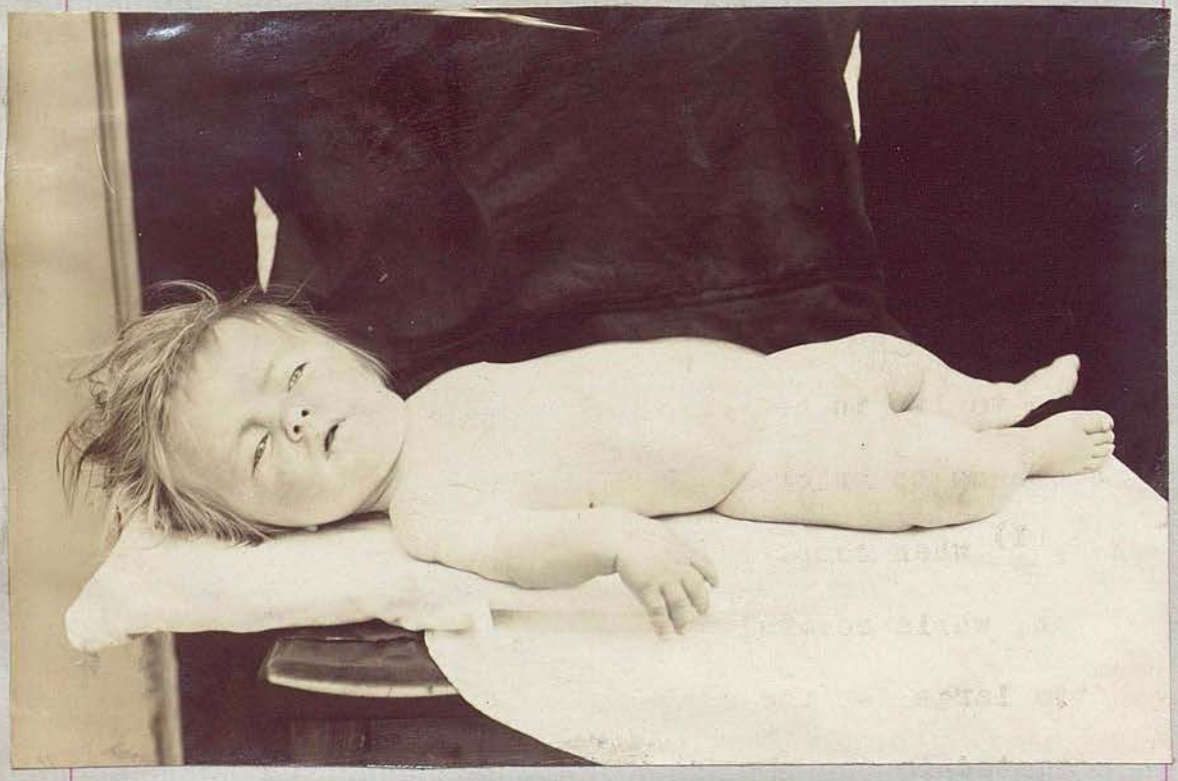

PLATE I.

the spine in that region were diminished. In a lateral direction mobility was good.

The most striking feature when we look at such a baby is the relative and absolute shortness of the limbs. While normally the umbilicus is roughly speaking, situated about half-way between the crown of the head and the soles of the feet, the middle of the long axis is here much higher, in the region of the tip of the xiphisternum

The lower limbs are not only short but very stout and there is a great amount of subcutaneous fat which, combined with an ample and loose skin, causes the soft tissues to lie in heavy folds, producing in the thighs a resemblance to knickerbockers. Kaufmann quotes Schidlowsky(1) when comparing the shape to that of an intussus ception, while several authors suggest that the soft parts are too large for the skeleton. This point is well illustrated in the skin-outline in Plate 2. which is a skiagram of Dorothy's lower limbs. This excess of subcutaneous fat is general and not confined to any particular situation and has been commented upon in all cases of the typical form of the disease.

The arms are also much shortened and while normally the finger tips in babies reach to about the middle 1/3 of the thigh, here they barely reach the upper border of the great trochanter and often fall far short of that.

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(1) Schidlowsky. Ueber sogenannte foetale Rachitis. Bibl. 35.

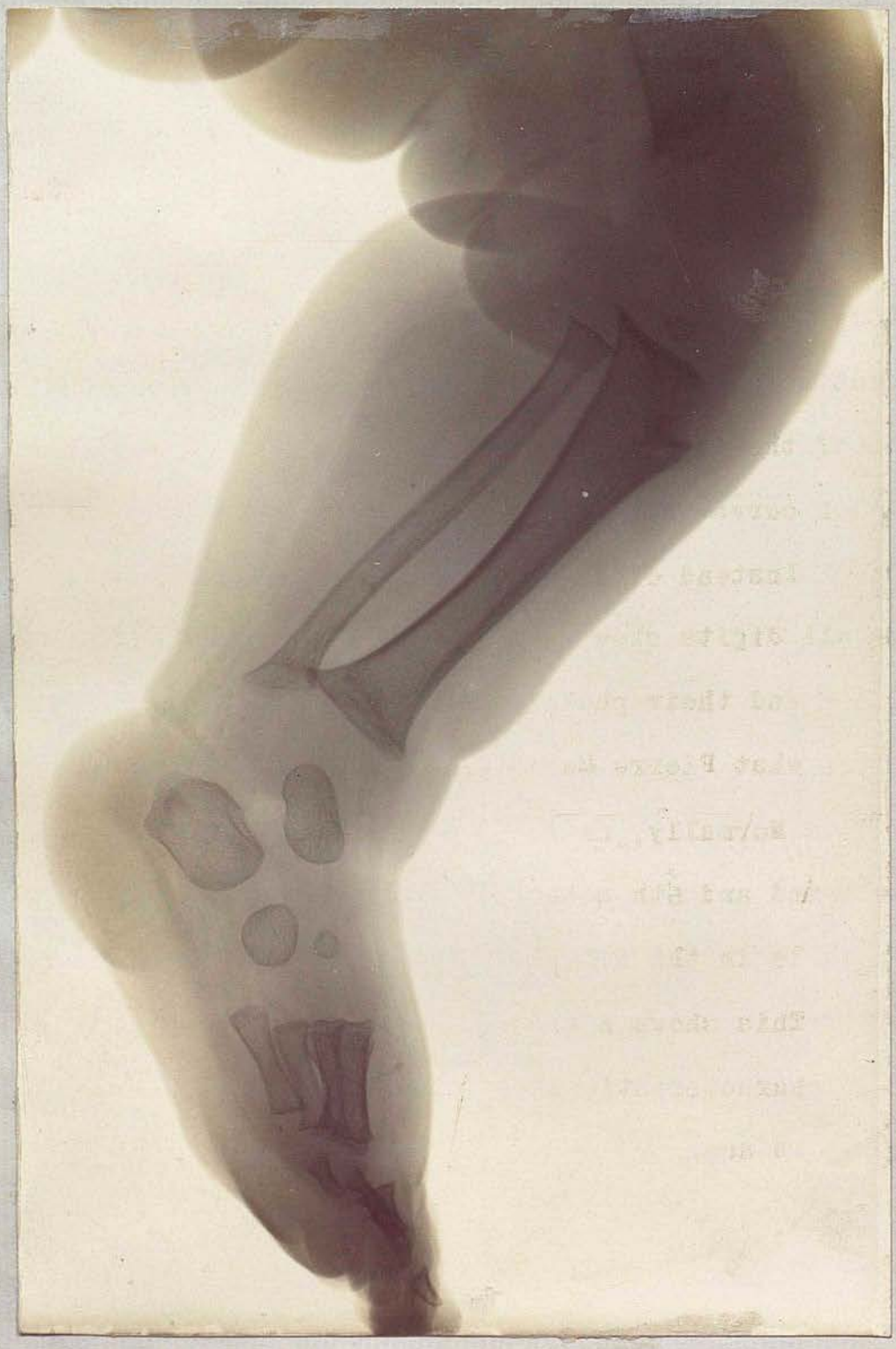

PLATE 2.

But the most characteristic feature is the hand, the shape of which is pathognomonic of this type of the disease and persisting throughout life as it does, and being quite marked in even very mild cases, appears of all the signs in the living subject, to be the most reliable. The hand is short and square and looks clumsy and heavy. The fingers are short and stumpy and if not actually of the same length, the line uniting the tips of the four inner fingers tends to show a much smaller curve than is normally the case. But there is more. Instead of showing the curve which in the normal hand all digits show towards the third finger, the metacarpals and their phalanges form divergent rays, thus causing what Pierre Marie(1) described as "main en trident". Normally, as Jansen points out, the long axes of the 2nd and 5th metacarpals form an angle of about 32°, while in the achondroplast hand it becomes 40° or more. This shows a tendency towards the persistence of foetal characteristic as a wide divergence of the metacarpals is seen in the newly formed foetal hand(2). All the changes are well illustrated in Plate 3.

At first sight the trunk looks fairly normal but on closer observation a few abnormalities are seen. Although the chest is narrow at its inlet the shoulders are rather

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(1) P. Marie. L'achondroplasis dans l'adolescence et dans l'age adulte. Bibl.52.
(2).Keibel & Mall. Handbuch der Entwicklungsgeschichte. etc. Bibl. 83.

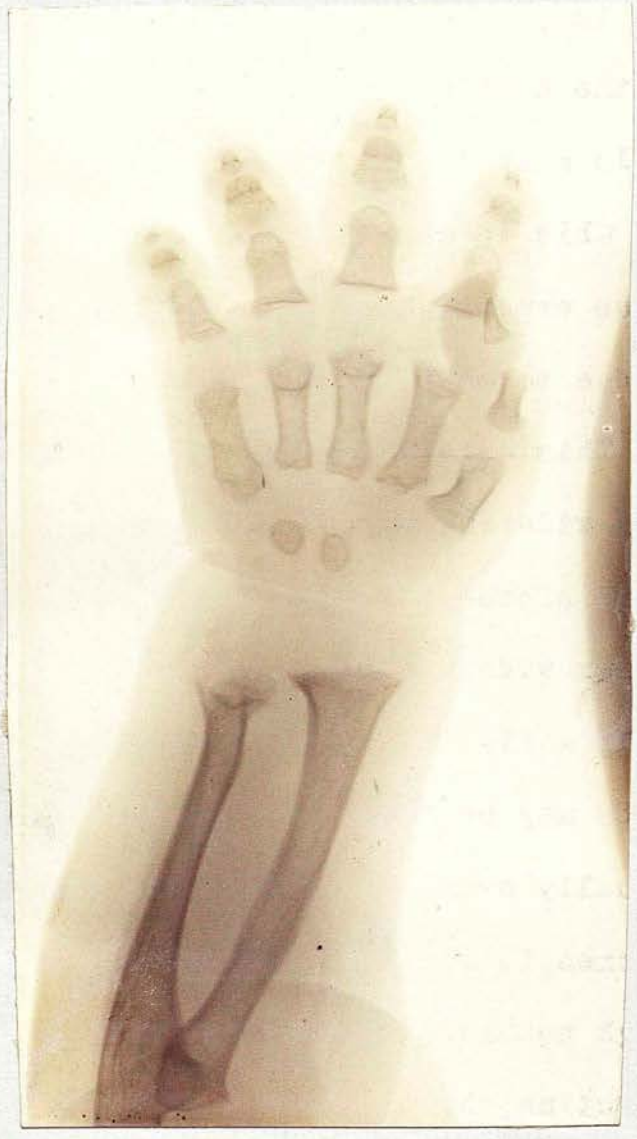

PLATE 3.

broad. This is more apparent than real. The distance between the tips of the acromion processes is usually but little diminished but the almost normal shoulder girdle seems large when compared with the narrowed pelvis and this is the most potent factor in giving us this impression. In many cases the arms are held somewhat abducted and this is mainly seen in those cases where there is undue expansion of the head of the humerus and is probably due to mechanical interference with complete adduction. This enlargement of the epiphyses and corresponding widening out of the bony diaphysis in those cases is a cause of real broadening.

The thorax widens towards its outlet and often a rosary is felt while in bad and usually non-viable cases the lower ribs may be pushed out to such an extent that they are actually overlapping like the tiles of a roof.

The abdomen is usually prominent. An umbilical hernia, though not infrequently met with, is, unlike what is seen in cretins, by no means a constant feature.

The pelvis is distinctly narrow; the cause of this is to be found in skeletal changes which will be described later.

It has been the custom to describe the back as showing no abnormalities in children who had not walked, while in older patients a marked lordosis has drawn

universal attention. Jansen[1] however, shows in all his cases, ranging in age from 2 (when the patient had never even sat up) to 22 years and in the foetal skeletons he describes a kyphosis of the dorso-lumbar region which is more obvious when the patient lies on his side but which is always present, though in older subjects lordosis caused by a tilting-back of the pelvis, masks it. In the patient, Dorothy P. it was actually the symptom the child was brought up to the Hospital for and in a case of the hyperplastic variety, to be more fully described later, spinal deformities became one of the most noticeable features.

In all cases the heads show great similarity, both in shape and in facial characteristics.

The face has been called "cretinoid" and the depressed bridge of the nose, the bulging forehead, the often somewhat thick lips, in the dead-born foetus frequently a protruding tongue and the abundance of subcutaneous tissue certainly recalls the cretin. But as Dr. John Thomsom says,[2] it is the face of the grown-up cretin which is seen in the achondroplastic foetus. The newly born child which is fated to become a cretin shows no characteristic facies. This is only what one would expect as the secretion of the maternal thyroid

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(1) Bibl. 88. pg.66
(2) John Thomson. Clinical Examination & Treatment of Sick Children. Bibl. 76A. pg. 491.

appears to suffice for the foetus till the beginning of a separate existence. But the similarity to cretinism is only superficial. There is no dryness and scaliness of the cutis and the finer wrinkles seen in the latter condition are replaced by heavy folds of skin and subcutaneous fat. The growth of hair is usually abundant and if the achondroplast lives, the intellect develops normally and sexual development is enhanced instead of absent.

In shape the head is markedly brachy-cephalic and the circumference is large. Cautley[1] states that it may equal the total body length. The face remains small and the result of the difference in width at the upper and lower part produces in many cases what Porak[2] called a "pyriform" face. The anterior fontanelle is usually large and remains open for a period exceeding the average. Prof. Keith[3] has pointed out that the anterior part of the skull is much better developed than the posterior which results in marked fronto--cephaly viz. a condition of frontal protrusion or projection. One or two observers have mentioned that in quite young children pubic hairs may be present as in a case described by Jansen[4] where a two-year old girl had a

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(1) Bibl. 85 loc.cit.
(2) Porak. De l'achondroplasic.etc. Bibl.40
(3) Arthur Keith. Abnormal Crania.etc. Bibl.94.
(4) Bibl. 88. pg.27.

PLATE 4.

number of well-developed hairs on the labia majora "exactly corresponding with such as are seen normally only at the beginning of puberty", while the same author quotes a case, recorded by Swoboda, of a ten year old girl with "abnormally strong hair growth".

The intellect of those children is generally not or only slightly impaired. It is true that the art of walking and even of sitting up is acquired later than in the healthy child but in the presence of other signs of developing intellect one may assume that this is due to the actual physical difficulty of supporting the heavy head and of locomotion in this top-heavy body.

It may be added that in adult subjects the general appearance indicates that in the typical cases there has been post-natal growth which, though it may have been somewhat retarded, approaches the normal as nearly as is possible in a body showing such marked deformity at the time of birth. The lordosis which becomes so pronounced is there potentially at birth and it is only after assuming the erect attitude that it becomes visible. Plate 4 is a photograph of Irene B. aet 2 years and 8 months, and shows the appearance of an achondroplast about this time of life. The muscular development, which is usually very good, requires large bony attachments and that in the stunted bones accentuates the deformities.

In one respect there is actual improvement: the

marked obesity tends to disappear, usually more so in the male than in the female. But as childhood is left behind, sexual desire manifests itself in those subjects in an abnormal degree and the external sexual organs and secondary sex characteristics attain a development above the normal.

Most observers are struck with this peculiarity, and Marie[1], Apert[2], Parhon, Shunda and Zalplachta[3], Jansen[4] and many others give instances. Parturition is, by reason of the pelvic deformities, of course attended by very grave risks and yet this does not prevent frequent exposure to these dangers even though the female achondroplast's chances of marriage are small. Jansen mentions the case of an unmarried achondroplast dwarf who underwent Caesarian section on four occasions. Sometimes the offspring show the disease, more often the children are normal.

The intellect may become quite good but there is often a certain coarseness of thought and roughness of wit, which, combined with a marked degree of boastfulness and vanity, may have stood them in good stead in the days when they found a lucrative occupation as Court dwarfs and jesters.

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(1) Bibl. 52. loc.cit.
(2) E.Apert. Quelques remarques sur l'achondroplasie.etc. Bibl.55.
(3) Parhon, Shunda & Zalplachta. Nouv.Iconogr. 1905.
(4) Bibl. 88. loc.cit. pg.27.

In this city I know of a male achondroplast, about thirty years old, who holds a responsible position, in which he is apparently successful, who is a habitué of a certain much frequented tea-room, where he occupies as prominent a position as he can find, and who is obviously as interested in the lady visitors as he is pleased with the attention his unusual appearance naturally attracts.

PATHOLOGICAL CHANGES.

Let us now see what are the actual morbid changes in uncomplicated cases.

The Skeleton.

Skull. Here we find ourselves on dangerous ground because there is a great deal of difference in the way various observers have interpreted the changes noted and even in the observations themselves.

In fact, although the facial characteristics are so similar as to suggest a strong family resemblance amongst the subjects affected, and although because of this one is apt to suspect a uniform lesion at the base of the skull there is only one main feature common to all and that is a diminution in length of the base of the skull and posterior fossa. There are however, many different

ways in which this shortening may be brought about.

In the case already mentioned of a "newly-born cretin who already possessed the typical appearance of this pathological race" and which closely resembled the cases afterwards described as "so-called foetal rickets" Virchow took the changes in the os tribasilare as the key to the changes in the physiognomy. In this case the tribasilar bone, consisting of pre-sphenoid, basi- or post-sphenoid and basi-occipital, was found to be shortened by about 1 cm. in a foetus having a total length of 33 c.m. Along with this a synostosis had already formed between the basi-sphenoid and basi-occipital(1).

The normal state of affairs is as follows(2,3):- the pre-sphenoid and post-sphenoid are both originally derived from the trabeculae cranii. About the third month of embryonic life the basi-sphenoid shows two ossific centres lying ventral to the pituitary fossa. The inter-sphenoidal synchondrosis is partly ossified at birth without being entirely closed and remains of the synchondrosis can be found till about the 15th year. The spheno-occipital synchondrosis persists for a long time; complete synostosis takes place about the 18th or 20th year.

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(1) Bibl. 13 & 15.loc.cit.
(2) Cunningham. Text-book of Anatomy. Bibl.60A.
(3) Arthur Keith. Human Embryology. Bibl. 65A.

Now, although by many observers the premature synostosis was supposed to be the determining factor of the facial deformities, it soon became obvious, as in fact Virchow himself pointed out, that this early fusion by itself could not be the sole cause.

A mere shortening of the base of the skull but without ossification of the sutures occurs in some undoubted cases of achondroplasia. In some ossification of the os tribasilare is even backward, while cases are actually on record where the bone was not shortened at all.

Kaufmann who carefully measured and examined thirteen foetal skulls found synostosis with shortening of the tribasilar in six only. In two the intersphenoidal as well as the spheno-occipital synchondrosis persisted while the shortening had mainly affected the structures developed in that part of the trabeculae which fuse anterior to the original cranio-pharyngeal canal. In three cases not only was synostosis between the component parts of the os tribasilare absent, but the ossification of the whole structure was much behind the normal and the cartilage was so soft and badly formed that it was impossible to define the exact limits of the ethmoid and nasal septum on one side and the presphenoid on the other. In Cases IX and XI[1] of this series little or no shortening

(1) Bibl. 43. loc.cit. pg.30.

of the tribasilar bone had taken place and yet the features were those of the typical achondroplast.

Another point stated by Virchow was that the angle formed by the planes of the basi-occipital and the sphenoid is diminished. This angle increases from the 3rd month of embryonic life till birth when it measures on an average 155°, while from then until puberty it gradually gets smaller again(1). This diminution of the sphenoidal angle has been called a kyphosis of the base of the skull. But again, this is not an unvarying rule and in one case at least(No. VI) in Kaufmann's series, the angle is not only larger than usual but the two planes in question have practically become one. There however, the whole plane approaches the vertical too much and this peculiarity seems to be constant in the basi-occipital. But there are also changes in the vertical axis of the face and the distance between the nasion and the alveolar point is always diminished, while the nasal septum is lower than it should be.

All these observations can be verified by studying the sagittal sections of the skulls reproduced and the measurements mentioned in Kaufmann's book.(2)

In only one of his cases are the diameters of the foramen magnum given and that is in Case V. which has not

(1) Bibl. 15. loc.cit.
(2) Bibl.43.loc.cit. pg.Tab.III. pg.35. Taf.III & IV.

been considered in the above description as it is obviously not an uncomplicated case of chondrodystrophy. It measures 1.7 x 1.8 c.m. in a 40 c.m. foetus. In Prof. Keith's[1] article quoted, the foramen of a normal full time foetus is shown as 1.8 x 1.8 c.m. so that in the case mentioned there is no diminution. But in the diagrams of Cases I and II they seem certainly very much shortened sagitally, while in the other two skulls of which a section in that plane is reproduced (Cases VI & VIII) there seems to be little or no change. This point is of interest because Prof. Keith[1] lays much stress on this deformity and finds it in all the skulls he describes, both young and adult ones.

Lampe[2] recorded a case where the medulla oblongata was squeezed together and destroyed by a foramen magnum of only 2 m.m. antero-posterior diameter, and Jansen also calls attention to its sagittal shortening but points out, as Porak and Durante[3] did before, that it is not a constant occurrence. Another observation he makes is that in those cases where the sphenoidal angle is much diminished, the antero-posterior diameter of the foramen is also unduly short, while where there is little or no diminution in the angle, the foramen approaches the normal in size. Thus in Kaufmann's cases I and II

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(1) Bibl. 94.
(2) Lampe. Ueber zwei Fall von sogenannter foetalen Rachitis. Bibl. 48.
(3) Porak & Durante. Les micromelies congenitales. etc. Bibl. 71.

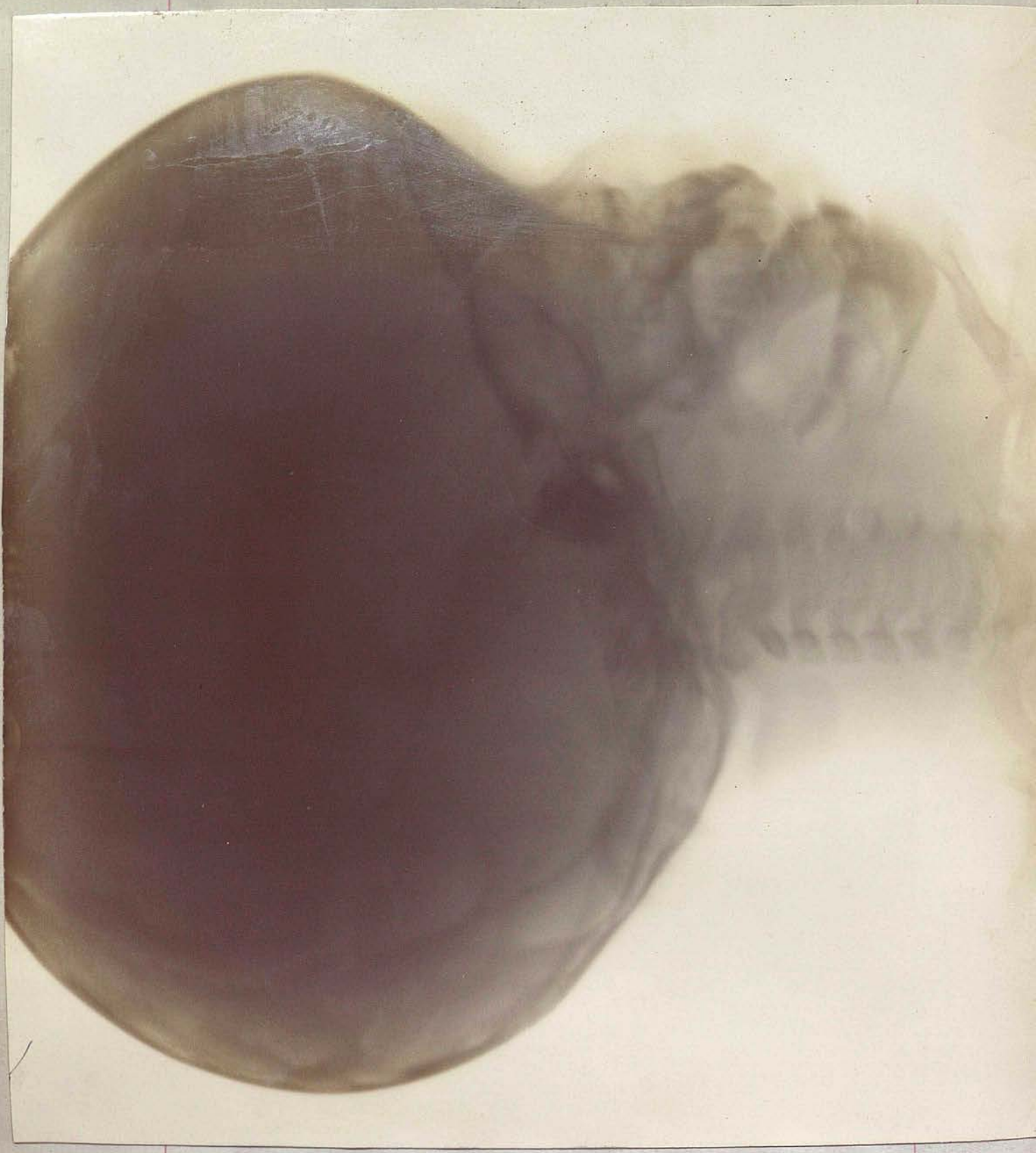

PLATE 5.

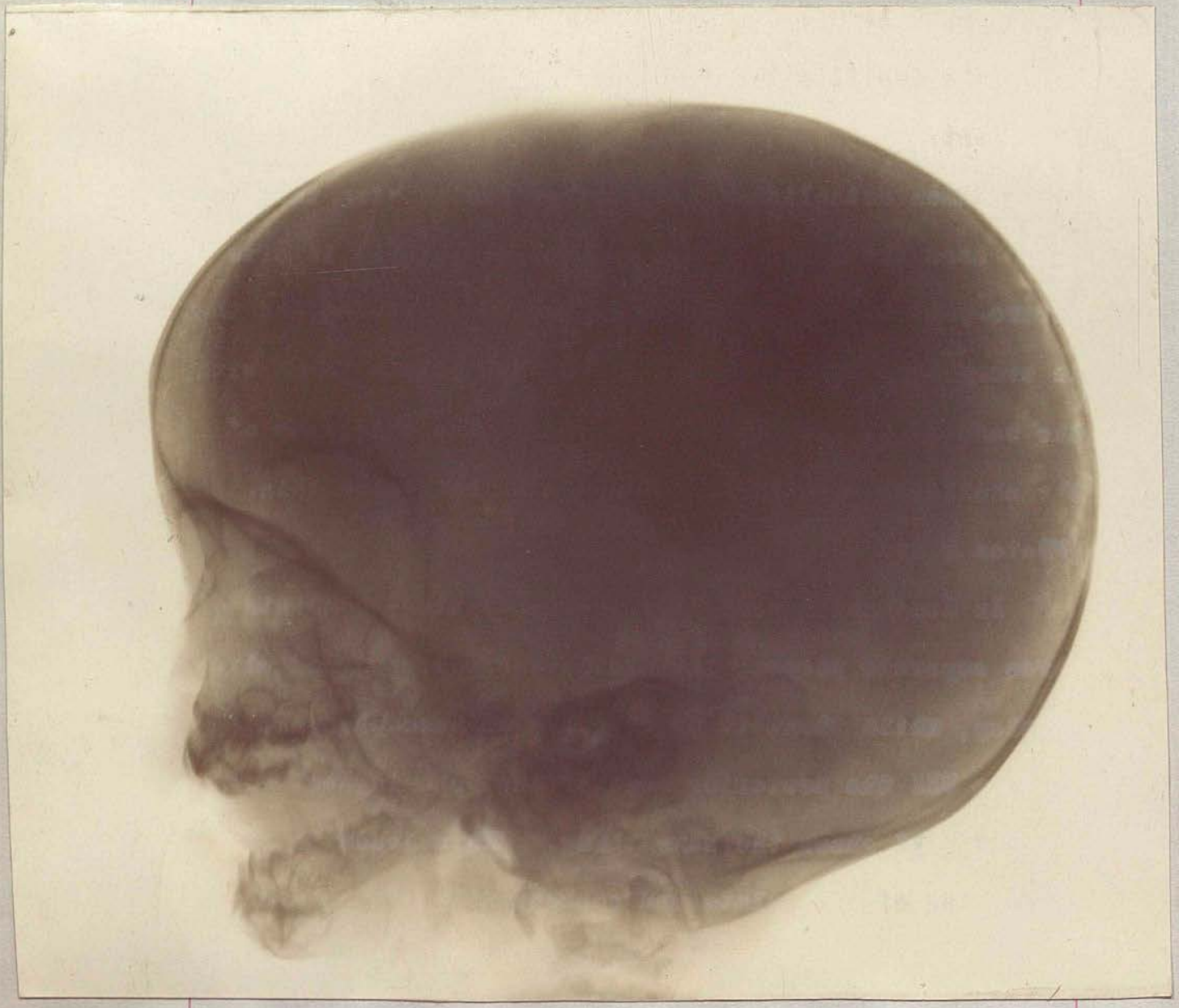

PLATE 6.

the angle is respectively 114° and 117° as compared with the normal 155° and the foramen magnum appears very small, while in cases VI and VIII, with angles of 160° and 140°, the foramen shows a normally long sagittal diameter. It may be mentioned that in these latter cases the ossification of the tribasilar bone is deficient.

Jansen establishes two further facts, viz. that in many cases the naso-pharynx is much diminished in size antero-posteriorly and the hard palate shortened and that in every case the angle which the hard palate forms with the base of the skull is increased. The skiagrams of the skulls of Dorothy P. and James R. both show this. (Plates 5 and 6).

In Kaufmann's case VIII the hard palate consists of three separate pieces, the middle and posterior of which overlap, while there is practically no naso-pharynx. In case VII the posterior edge of the bone is bent down while No. VI shows the same thing. This leads to a shortening of the palate and consequently of the oral cavity. In many cases the palatal deformity and the resulting encroachment on the naso-pharyngeal space gives rise to a noisy respiration which was very marked in James R. (vide infra) and which in one of Dr. Jansen's cases led to an operation for the removal of supposed adenoids, which of course did not relieve the symptom.

It is interesting that Kaufmann, although not remarking on the deformity of the palate, groups cases VI, VII and VIII together as showing a general flattening of the nose instead of the usual depression of the bridge only, and that, as we saw, in all those the naso-pharynx is excessively small; the patient selected by Dr. Jansen to demonstrate the palatal deformity shows this same flattening of the whole profile. Kaufmann mentions another skull, that of case XIII, which shows the flat side view but he does not describe it fully. He states however, that synostosis of the tribasilar had taken place. In cases VI, VII and VII there was defective ossification of that bone with much softening of the cartilage and he took this to be responsible for the difference in the facial characters as compared with the other cases. The findings in case XIII show this to have been a wrong conclusion. Unfortunately there is no record of the naso-pharyngeal dimensions and thus we cannot test the view that the flat profile is a result of shortening of the palate and contraction of the naso-pharynx in this case.

A constant feature is a diminution in the size of the pituitary fossa(1). This is always present but seems to occur in inverse ratio to the gravity of the condition. In a non-viable foetus it may be extremely

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(1) Arthur Keith. Progeria & Ateleiosis. Bibl.92.pg.308.

small. In a case mentioned by Jansen[1] of an adult woman who was almost normal except for slight stunting of the humerus and femur but with characteristic shortening of the base of the skull without, however, producing an achondroplastic type of face and so little pelvic deformity that she had had several normal confinements, the pituitary fossa was"of normal size or very nearly so" The fossa is reduced in all dimensions and not mainly in a sagittal direction.[2,3]:

But the changes are not all confined to those parts of the basis cranii lying anterior to the foramen magnum. The condyles are usually deformed, their posterior parts splayed out. The jugular foramina may be reduced to mere slits. The supra-occipitals which are formed endochondrally show great stunting and the posterior fossa of the skull is hence much diminished in depth and does not afford sufficient space for the normally developed cerebellum. The squamous part of the occipital bone has to step into the breach and must provide space. The tentorium cerebelli has to be attached much higher and may reach to the lambda[4]. A compensatory expansion of the rest of the cranial vault is a further result and the brain grows upwards and forwards, and what Jansen

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(1) Bibl. 88. loc.cit. pg. 44.
(2) Bibl.92. p. 308.
(3). Bibl. 88.
(4) Bibl. 94.

calls "kyphosis of the brain" occurs. The frontal bone is carried forwards and bulges outwards. Prof. Keith takes this to be the cause of a depression of the ethmoidal and orbital plates with increased angulation at the junction of basi- and pre-sphenoid. He also holds that "the appearance of nasal retraction.....is largely due to the bulging of the forehead(1).

To sum up: the skeletal changes in the young skull are very varied but there is found constantly -

1. A shortening of the floor of the skull in which all componant parts may share or from which some may escape.

2. A corresponding increase in the dimensions of the vault, mainly in a forward direction.

3. A strong tendency of foramina and cavities to join in the diminution of the antero-posterior diameter which they can only escape by a change in the direction of the neighbouring bones and in the angles these form with each other.

4. A general diminution in the size of the pituitary fossa.

5. A shortening of the vertical length of the face(2).

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(1) Bibl. 92. pg. 191.

(2) It must be mentioned that Prof. Keith states (Bibl.94 pg.194) that "the ethmoidal cartilage is normal in size. The perpendicular plate is certainly diminished in height in several of Kaufmann's cases. It is not so easy to verify the long diameter but in cases VI VII & VIII there is very distinct shortening of the nasal septum as a whole. Whether this does not include the perpendicular plate of the ethmoid is a point we cannot decide on the data we have. It seems probable that this part of the skeleton, like all the rest,varies very much in individual cases & even though the case illustrated in Fig.4 in the article mentioned does not show any interference with the nasal septum,one feels hardly justified in generalising from it.

Spinal Column.

It has been customary to describe this structure as normal and most text-books still mention this as a fact and some even lay special stress on it and contrast it with what is met with in rickets. There are however, changes both in the individual vertebrae and in the spine as a whole.

First of all there is the dorso-lumbar kyphosis which has already been mentioned and which seems to be a much commoner deformity than is generally accepted. Jansen takes it to be of universal occurrence in all cases of the disease(1) and makes it an important point supporting his theory of pressure as the cause of the disease. In every patient and illustration which I have seen there certainly is some degree of antero-posterior curving in the lower dorsal and upper lumbar spine having its convexity backwards and this would probably have been the experience of all those who have interested themselves in the disease, but for the fact that in living adult subjects the lordosis, due to pelvic causes, masks it and that in the cadaver of the newly-born infant or foetus post-mortem influences and position are so apt to obscure any slight arcuate kyphosis. And these are the two classes of subjects on whom most of the work has been done while living babies have been less often described. In Kaufmann's case VIII an angular kyphosis was noticed

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(1) Bibl. 88. pg. 49.

which was found to be due to deformity of the last lumbar vertebra the body of which was .8 c.m. high in front and 1.2 c.m. behind. This case however, was one of the same variety of which James R.s, to be described later, is an example and in his case there were very marked spinal changes.

In the second place the individual vertebrae show differences in their comparative size, chiefly in width which diminishes from above downwards, so that the usual picture, a diminution in width of the bodies to the 4th dorsal vertebra and a gradual widening out below this[1] is changed into a gradual narrowing from the upper cervical down to the lowest lumbar vertebra, thus producing an outline approaching an inverted triangle. Thus in the skeleton of an achondroplastic foetus measured by Jansen[2] the width of the third cervical vertebra was 14 m.m. as compared with 18.4 m.m. in a normal skeleton of the same age, while the 3rd lumbar was 12 m.m. against the normal 18 m.m. In a smaller skeleton showing the changes in a severer degree of the disease the same sort of thing was found.

At birth the ossific centres are rarely normal. More often they are irregular in shape and position and they are almost always smaller than normal. Premature fusions of the ossific centres of the vertebral arches

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(1) Bibl. 60A. pg.86
(2) Bibl. 88. pg. 19.

and bodies and some narrowing of the neural canal has been noted by Sumita(1) and others.

Thorax.

The inferior end of the sternum is usually displaced forwards and in non-viable cases it has been observed to take up an almost horizontal position. With this is necessarily associated a vertical shortening of the whole thoracic cavity and a widening of its outlet. The lower ribs are pushed out and may even override the one immediately below. Obviously in cases of that degree of severity the thoracic viscera have not been able to find sufficient accomodation inside the cavity to allow for expansion of the lungs.

In milder cases the sternum approaches the normal. Although it is usually backward in its ossification it is not much deformed. The ribs often show a considerable shortening so that the costo-chondral junction comes to lie nearer the angle of the rib and the cartilaginous part is longer in proportion. A "rosary", if not always present, is of frequent occurrence. But it is formed in a manner somewhat different from that causing the rachitic beading. Two factors are operative in producing the thickening. The first is an actual displacement with angularity at the osseous and cartilaginous junction in

(1) Sumita. Beitrage zur Lehre von der chondrodystrophia foetalis. Deutsche Zeitschr.f. Chirurgie.

in such a manner that the cartilage grows past the osseous part and then, by a sudden kink inwards, gets united to the bone. In Kaufmann's case II it actually doubles back on itself and the anterior extremity of the bony rib and the posterior one of the cartilage may thus come to lie side by side for a short distance. The effect of this is more noticeable on the pleural surface of the costal arch.

Apart from this and sometimes co-existing with it, is a widening and expansion of the bony element which forms a funnel or cup-shaped extremity to the bone for the reception of the cartilage. The interior of this cup sometimes shows a lamellar arrangement so that thin shells of bone can be easily detached, diminishing in size from without inwards and fitting each other very closely.(Kaufmann's case V.) As we shall see later this cupping of bony extremities is seen in all the long bones.

Shoulder-girdle.

The scapula shows the stunting which is so prominent a feature in the long bones but to a lesser degree. In most cases the cartilaginous element preponderates and ossification is backward.

The clavicle, however, suffers less than any other bone in the body. This is a very interesting point and will be referred to later. In Kaufmann's series(1) the measurements of these clavicles are given(1). One is

(1) Bibl.43 pg.43 Tab.II.pg 36.

that of a 38 c.m. foetus in which the bone is 4 c.m. In another, with a total body-length of 38 c.m., a 3.7 c.m. clavicle was present, while in only one does he find a length of 2.6c,m, but this foetus was only 24 c.m long. The average length in a foetus of 50 c.m. is 4 c.m. The ossification is also well advanced and in every one of Kaufmann's cases in which the clavicle is mentioned, the dense hardness of the bone is commented upon. The only deviation from the normal is the exaggeration of the normal curves which might quite well be explained by an attempt on the part of nature to approximate the width of the shoulder girdle to the narrow thoracic inlet. These findings are of great interest and importance as shedding some light on the nature of the disease and we shall discuss this point more fully when we come to speak of the true nature of the condition.

Pelvic girdle.

The bones forming this structure are amongst those more seriously crippled. The pelvis suffers in its general outline and in this way constitutes the most serious deformity in the adult female achondroplast. But it also fails to transmit the body_weight to the lower limbs in a normal manner, and so, in the grown-up subject of either sex, accentuates the other deformities, producing the lordosis mentioned before which is the main

factor in causing the typical waddling gait.

Again, there is some difference in the nature of the deformities in different cases. In the ilia the commonest departure from the normal seems to be a deviation of the plane so as to bring them more parallel to the coronal diameter than usual. There is also a diminution of their normal slope outwards and they tend to take up an almost vertical position. Along with this is found a general flattening of the bone which may or may not show some cartilaginous overgrowth and eversion of the crest.

The ischia are stunted to a much greater degree than the ilia[1] and in the non-viable foetus the height of the pelvis is much more diminished than its breadth. In some pelves the ischial tuberosities are especially small.

The acetabulum is sometimes fairly deep while in other cases it is seen to be quite shallow. In cases where the head of the femur is much enlarged we get an almost flat receptacle for it and thus we have what practically amounts to a dislocation.

The pubic angle is **very** acute as a rule.

The promontory of the sacrum is often difficult to define exactly. Usually the sacrum itself sinks more deeply into the pelvis and its plane approaches the

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(1) Bibl. 88. pg. 73.

horizontal too much. The sacral curve is usually flattened. Ossification is delayed.

The pelvis as a whole shows a persistence of the foetal type and remains more or less funnel shaped in adult life. The inlet is usually of a triangular shape and is more or less contracted. The outlet is relatively wider. Often asymmetry is added to this contraction which is a result of a pushing in of one of the acetabula into the cavity of the pelvis.

On the whole, as already stated, there is great variation in the changes seen in individual cases and in young pelves only few resemble each other closely, although though they never escape serious deformity. The changes mentioned can be verified from Kaufmann's descriptions.

But one feature they all have in common. In consequence of the smallness of the ilia the acetabula are placed too far back. A result of this is that inthe erect attitude the line of gravity passes in front of them and hence there is a tilting forwards of the pelvic inlet and a postural lordosis which is emphasised by the abundance of soft tissue in the gluteal region.

The limbs.

The deformities are practically the same in the upper and lower limbs except for the fact they they are more marked and that the stunting is more complete in the latter. The limbs are rhizomelic as opposed to

mesomelic, in other words, the proximal segment suffers more than the middle one but this is not invariably so[1].

On examining a long bone one immediately notes the difference between it and a rickety bone. Here the deformity is more angular while in rickets one finds curvatures. The angulation occurs almost entirely at the epiphyseo-diaphyseal junction, for, although the epiphysis, at least macroscopically, is only deformed in the sense that the normal anatomical outlines are not defined clearly, the morbid growth in cartilage, which is so highly characteristic of the disease, has irregularity of cell-proliferation as one of its prominent features.

The result of this is a deviation of the axes of epiphysis and diaphysis. This explains why, unlike what occurs in rachitis these deformities are present and in some cases most marked before body_weight or faulty position can have been a factor in their production.

Whether or not intra-uterine muscular action plays a part in determining the nature of the deformity is a much debated point. Jansen[2] seems to think it does. He bases this view on an observation made by Pierre Marie[3] viz. that the fibula is lengthened in proportion to the tibia. The former observer says:- "It should be re-
"membered that the tibia is held under constant pressure

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(1) Dr. Poynton. Achondroplasia. Bibl. 75A.
(2) Bibl.88. pg.24
(3) Bibl. 52. loc.cit.

"by muscular action, even before birth, and after birth "much more so in the acts of standing and walking; "whereas the fibula which serves chiefly for the attach-"ment of muscle, is much less affected - if at all - by "presence of either the body weight or muscle-action. "Hence it seems that the normal function of the bone "substance is able to accentuate the dwarf symptoms: its "specific faculty, viz. of growing against the pressure "of gravity and muscle action, is diminished in achondro-"plasia". One cannot help thinking that it is very doubtful if the fibula is less supported by the pressure of muscles surrounding it than the tibia. The latter with its subcutaneous surface along the whole length of the bone appears the one least firmly supported all round its circumference. Then, if muscular action were as important a factor as other observers (e.g. Kaufmann[1]) take it to be, the deformities would seem more likely to present a greater uniformity in different cases than is actually met with. The only fairly constant deformity seems to be the disproportion in length between them which is also, but much less frequently, seen in the forearm[2]. It must be admitted that Kaufmann[1] notes that in no cases known to him was the tendency to reproduce the physiological curvatures of the femur in the pathological angling and curving quite hidden. He

(1) Bibl. 43 pg. 56
(2) Bibl. 81.

therefore takes the view that muscular action and the position of the limb in utero produce the deformity. He supports this theory by pointing out that in those cases where the cartilage was found to be unduly soft, angulation was most marked. It seems natural to assume that the morbid process, whatever its nature may be, has acted most intensely in those cases where the cartilage remains softest. There can also be little doubt that in a bone where the small ossified and rigid part is completed above and below by disproportionately large cartilaginous masses, any position in late foetal life will leave its mark on its ultimate shape. But in our opinion it has been proved by Jansen (we shall refer to this point later) that the deformities must have originated long before mere position in utero could be regarded as the sole cause. Then if we look at what has been found in the ribs we observe an angling which may actually develop into an acute kinking at the costochondral junction, a deformity which neither muscular action nor malposition could possibly produce.

Porak and Durante[1] maintained that sometimes the diaphysis itself may show an angular deformity and even state that the time at which it arose may be roughly calculated from its distance from the line of ossification. Instances of this acute bending in the diaphysis

(1) Bibl. 71.

are very rare. Curving of the shaft without angulation is probably in most cases more apparent that real. The planes of the epiphyseo-diaphyseal junctions at the proximal and distal ends of the long bones rarely run parallel in achondroplasia. Yet, instead of causing the curving along the diaphyses one would expect from such a state of things, the result is a buttressing up of the epiphyses on that side where the two planes approximate each other most and where as a result support is most needed. This causes an irregular mushroom-shaped expansion with the result that the inner margin of the shaft may approach in shape the arc of a circle while the outer, except for some broadening near the line of junction of bone and cartilage, remains almost straight. The long axis of the diaphyses remains thus perfectly straight. This is beautifully shown in Plates 8, 11 and 19.

At the epiphyseal line the same change is seen as has been described when dealing with the costo-chondral junction. The bone ends in a somewhat irregularly bell- or cup-shaped cavity which receives the epiphysis. This peculiar shape of the diaphyseal extremity is quite characteristic of achondroplasia and even in mild cases it can be seen in skiagrams which thus help us to diagnose doubtful cases where it used to be held that nothing short of a microscopical examination of the epiphyseal cartilage could clinch the diagnosis.

The epiphyses are as a rule enlarged in all

dimensions and may be quite irregular in outline. The articular surfaces may be very difficult to define but in most cases the head of the humerus and that of the femur are enlarged and where this is moderate, may fit a correspondingly deep cavity. Where the enlargement is excessive the much flattened glenoid cavity or acctabulum may only be in contact with a small part of the surface of the head at the time.

The ossification of the carpus and tarsus lags much behind the normal. The metatarsals and still more the metacarpals show the exaggerated divergence mentioned before.

The phalanges are much shortened and broadened and may be square. (See Plate 3).

"Periost-fortsatz".

A description of the naked-eye appearances of the skeleton would be incomplete without mentioning the peculiar arrangement of the periosteum at the junction of bone and cartilage which Kaufmann speaks of - the "Periost-fortsatz"(1). He notices it macroscopically in 8 cases out of his series and mentions that it may differ very much in thickness in different cases and even in individual bones of the same subject. In some cases it can only be made out microscopically while in some

(1) Bibl. 43. pg. 53

bones no traces can be seen even after careful examination

It consists of a projection of the investing layers of the bone and cartilage into the epiphyseo-diaphyseal junction and usually thins out towards the centre of the bone but may actually separate the epiphysis completely from the shaft.

Kaufmann states that "wherever the periosteal pro-"cess has insinuated itself endochondral bone development "has been put a stop to; growth in length ceases; only "where bone and cartilage continue to be in direct con-"tact can we speak of growth in length by endochondral "formation of bone". He further remarks that the thickness of the periosteum bears a direct ratio to the denseness of the periosteal bone and expresses the opinion that this points to the possibility of the peri-osteal intrusion being the result of excessive growth of the investing membrane.

To avoid repetition I shall here give a short description of the microscopical characters of this periosteal lamella.

It consists of fibrous tissue, containing many spindle-cells and is continuous with the periosteum and perichondrium. Embedded in it are many vessels of considerable length. Towards the centre of the bone it diminishes in thickness til it loses itself in the matrix of the cartilage which for a little distance retains a somewhat fibrous character. In the cartilage itself

(which is to be described later) we find an area containing a few spindle-shaped cells which show an attempt at row formation and these appear to be to some extent a continuation of the periosteal ingrowth. Some vessels which run parallel to the zone of calcification in the cartilage are sometimes seen to be in direct contact with the fibrous tissue and can occasionally be made out to be actually continuous with the vessels thereof. In other cases vessels proceed from marrow spaces and anastomose at the outer limit of the calcifying zone with large branches of vessels in the epiphysis. These vessels are all accompanied by fibrous tissue and have very delicate walls. Where the periosteal lamella enters between epiphysis and diaphysis, the cartilage cells in the immediate neighbourhood take up a direction parallel to it and assume a spindle shape; the matrix of the cartilage becomes fibrous so that one cannot definitely say where the cartilage begins and the periosteum stops.

On the diaphyseal side the different appearances may be presented. Sometimes the connective tissue may change into true bone, following in every respect the normal development of periosteal bone. At other times, however, cartilage may be found on this side as well so that the process of periosteum actually protrudes into cartilage. In that case the diaphyseal side of the strip differs

in no way from the one already described. But in its deeper layers the cartilage gets gradually calcified and then ossification proceeds in the way seen in the normal diaphysis.

The manner in which the perichondrium or periosteum comes to lie in this abnormal position was and is still a matter of speculation. Eberth(1) holds that it is an inclusion. It is difficult to see how this could be the case as it is not invariably found in a situation where two anatomically or developmentally distinct structures join. Storp(2) considers it to be due to invagination of the investing membrane. The same objection holds here as exists against Eberth's view and besides, the histological appearances are not compatible with this view. Marchand and Kirchberg(3) explain it by an absence of endochondral ossification in the epiphysis, associated with progressive periosteal ossification and enlargement of the epiphysis. As growth in thickness proceeds that surface of the periosteum which was originally external comes to lie against the epiphysis and, as the latter structure continues to grow, it envelops the periosteum. Apart from the fact that if this be correct the "periostforsatz" must consist of fused perichondrium and periosteum which does not appear to be the case,

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(1) Eberth. Die foetale Rachitis,etc. Bibl.24
(2) Storp. Untersuchungen ueber foetale Rachitis.Bibl.36
(3) Bibl.39. loc.cit.

this view is based on a wrong observation; the periosteal bone overlaps the epiphysis and actually forms a cup for it which is the exact opposite of the condition assumed by Kirchberg and his collaborator.

Kaufmann[1] takes excessive activity of the periosteum itself as the cause. In his opinion a lateral displacement may occur as a result of arrest of growth in the epiphysis and increased proliferation of periosteal growth in the diaphysis. Into the angle formed the periosteum grows by means of an active proliferation of connective tissue, well supported by an abundant blood supply.

Judging from the actual histological appearances, much is to be said for this explanation. Undoubtedly the periosteum itself is not affected by any disturbance of growth, in fact it is thick and vascular. One can quite well imagine a periosteal covering which is out of proportion to the length of bone it envelops and which uses any pre-existing angle for its accomodation. It may also be active enough to penetrate into less vigorous and in this case, obviously abnormal tissue:- the cartilage. In the light of recent researches on the part the periosteum takes in the formation of bone and which will be referred to later, one cannot accept the whole of his contention - that proliferation of bone derived from a too active periosteum is partly responsible for the

(1) Bibl. 43. pg. 56

abnormal relative position of epiphysis and diaphysis. It seems likely that periosteum itself is not a bone former(1,2,3), and this is confirmed by what has been found in those places where the periosteal process has cartilage on its epiphyseal as well as its diaphyseal surface (vide ante) and where ossification on the latter side started in the layers furthest away from the periosteal tissue (vide infra).

We may assume then that the periosteum is growing very actively and actually grows into the skeletal tissues but there is no evidence that this results in the proliferation of bone which helps to cause the angulation at the epiphyseo-diaphyseal junction.

Microscopical Appearances of the Skeleton.

As I have not been fortunate enough to procure any material for microscopical examination, and hence in describing the minute changes, I shall give a short resume of Kaufmann's findings(4).

Long bones. At the junction of epiphysis and diaphysis a somewhat irregular fine line of division is seen, the specimens prepared stained blue with haematoxylin and eosin or carmin. This line represents the upper limit of the zone of preliminary calcification. The cartilage cells on the epiphyseal side of this line do

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(1) Prof. A.C.Geddes. The Origin of the Osteoblast.etc. Bibl.91
(1) Sir.Wm.MacEwen.Regeneration of Bone. Bibl.72.
(3) Ibid. The Role of the various elements in the Development and Regeneration of Bone. Bibl.76
(4) Bibl.43. pg.39.

not show a normal appearance but are mostly small and spindle shaped and contain an oblong, granular nucleus surrounded by clear cytoplasm. Sometimes these nuclei show a knob-like expansion in the centre or at one of the poles. The general arrangement of these cells is quite irregular. Where they approach the perichondrium and in some places near the diaphysis, they show a tendency to arrange themselves in rows at right angles to these structures. The zone in which this abortive attempt at parallelism is shown, is rather narrow and the cells taking part in it are flatter than usual. Nearer the zone of calcification the direction of these imperfect cell columns changes again and the cells themselves are now somewhat larger and rounder and their nucleus expands. This arrangement is all there is to represent the normal, regular formation of parallel rows of cells, invariably seen in ossifying cartilage(1). In some cases even this attempt is lacking and row-formation may be altogether in abeyance. When columns are found there are never more than 4 to 12 cells constituting them and the individual groups of cells are widely separated by broad strips of intercellular substance. This matrix is clear but shows a varying degree of density. Throughout the cartilage numerous oblong or round spaces are visible. These are surrounded by a somewhat more darkly

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(1) E.A.Schäfer. The Essentials of Histology.7th ed. London,1907.

staining matrix, containing cells which are less spindle shaped and may be arranged concentrically. Towards the periphery of this area and radiating out from it, larger cells which in appearance resemble those seen in the stunted cell columnsjust described, may often be seen. The central space contains somewhat oedematous mucoid looking connective tissue, poor in cells and showing many fissures. They contain thin-walled blood vessels.

The diaphysis shows great variations in different cases; while at one time the bone may be very dense so that there is practically no medullary cavity left, at others the whole shaft may show a spongy appearance,and although there is no continuous central marrow canal, there are many good sized marrow spaces, bounded by irregularly shaped bony trabeculae. The shape and thickness of the latter varies considerably.

Near the epiphyseal line these marrow spaces usually become somewhat longer and narrower but even in this respect there is no uniformity in individual cases. Occasionally these spaces encroach upon the vascular fibrous tissue spaces described above which gives an irregular outline to the ossifying border. Usually a marrow space forms a crescent shaped bay in the calcified and sometimes even in the uncalcified cartilage. Giant cells are seen to assist in this process of excavation and are fouhd in irregularly shaped hollows.

The trabeculae stain red with haematoxylin and eosin but in their interior we see blue staining material round which lies the red staining osseous tissue which shows the presence of lamallae. Where these differently staining processes meet, a layer of osteoblasts, which may reach a moderate thickness, is visible. Kaufmann takes the tissue staining red to be true bone and the non-lamellar blue core to be the remains of cartilage which is in process of ossification without there being any preliminary deposit of calcareous matter. He gives as his opinion that in the diaphysis there occurs an extensive direct ossification of cartilage the traces of which persist for some time under the new bony trabeculae. He finds it impossible to make any definite distinction between bone directly formed from periosteum, and that laid down by osteoblasts in the centre of the shaft.

The marrow is rich in round and spindle shaped cells and red corpuscles, and is plentifully provided with thin-walled blood vessels. Although the blood supply varies greatly, it is always abundant. In some cases excessive numbers of large multi-nucleated cells and typical giant cells are found.

A description of the ingrowth of periosteum has been given on page 37.

The ribs show changes similar to those in the femur but the blood vessels are still more numerous and the

matrix of the cartilage shows a larger number of spindle cells which givesit a somewhat reticular appearance.

Vertebrae.

Here, apart from a certain degree of softening of the intercellular substance of the cartilage, an interesting condition is sometimes seen. At the periphery of the intervertebral discs regular layers of fibrous appearance prevail; towards their centre a gradual separation of the individual fibres takes place. Some of these enter the adjacent vertebral bodies while others end in the centre of the disc where we find a light staining, finely granular, meshy ground substance through which course long, drawn-out cells with a cigar shaped nucleus. What we see are the remains of the notochord. Here, in some cases at least, the notochordal rests can be traced into the cartilaginous parts of the bodies of the vertebrae and the above picture is there complicated by the presence of large polygonal and round cells with clear contents. Marchand, who noticed this first, came to the conclusion that the situation of these rests inside the body of the vertebra points to a very early stage of ontogeny as the period of onset of the disease(1).

In Kaufmann's case VI, there actually exists a continuous strand of notochordal tissue through the

(1) Bibl.39 loc.cit. pg.210.

upper dorsal vertebrae. He concludes that the interference in this case must have taken place during the 7th week or anyhow "some time during the second month" of embryonic life(1).

These are the most important changes in the group of cases Kaufmann called chondrodystrophic hypoplastica and which correspond with what is usually known as "achondroplasia".

Minute Changes in the Hyperplastic Variety.

To avoid repetition we shall here shortly consider how the microscopical findings in the second group - chondrodystrophia hyperplastica - differ from the above.

Here there is a complete absence of any attempt to reproduce the appearances of normally ossifying cartilage coupled with a very marked excess in both the size and the number of the cell elements and the amount of intercellular substance; in other words, there is a true hyperplasia combined with an arrest of the changes normally preceding endochondral ossification.

In the centre of the epiphysis we find a marked increase of the intercellular substance which shows great vascularity. Round the vessels the matrix appears very soft and homogeneous. Only a few cells are seen here; these do not lie in groups and terminate at their poles in long processes. Nearer the calcifying zone the cell

(1) Bibl.43, loc.cit. pg. 44.

elements increase in number and size and may at last reach very large dimensions. They are so closely packed together that in this region the matrix is only represented by thin strip, staining red with haematoxylin and eosin. In Kaufmann's preparations the cells often shrink away from their capsules and are evidently very easily dislodged as several large holes are seen which are evidently empty cell capsules. These holes, only separated by very thin bars of matrix, produce the appearance of a network.

The blood supply is extremely abundant and this is seen even in the complete absence of any attempt at ossification as in the tarsus in Kaufmann's case VIII where no trace of bone can be found.

Softening of the cartilage is constantly present and this leads Kaufmann as well as Kirchberg and Marchand to suspect that this hyper_vascularisation starts at the process of softening.(1).(2). In cases of this class the periosteal ingrowth mentioned before is not of such frequent occurrence as in the hypoplastic cases.

On the diaphyseal side of the network just described we meet with a zone of extremely irregular calcification. The marrow spaces are sometimes directly continuous with the empty cell capsules. Here and there they are lined

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(1) Bibl.43. pg. 46
(2) Bibl. 38. pg. 210.

by red staining cartilage which in places shows irregular patches of calcification, while occasionally a lining of true bone may be seen. This bone may penetrate into quite unprepared cartilage in a manner similar to that described in cases of the hypoplastic type. Here and there bone invades calcified cartilage which appears as small islands. Formation of true bone lamellae in the presence of osteoblasts can be recognised quite distinctly in places.

Towards the middle of the diaphysis the bone appears dense, and is, according to Kaufmann, built up mainly by periosteal activity. The trabeculae show many osteoblasts on their surface. The inner layer of both periosteum and perichondrion is stated to be very cellular.

The marrow is very rich in cells which show a great variety of shapes and structure. We find round, elongated and spindle-shaped ones and the latter are frequently provided with long processes. Giant cells are numerous and lie often in little bays near the surface of the bone and, in this situation, give the impression of having been actively engaged in forming the hollow in which they are found. They are also seen, freely mixed with other cells, in the centre of the marrow. Red blood corpuscles occur in fairly large numbers but the blood vessels are few and far between; most of them possess fairly thick walls.

In case No.XIII of Kaufmann's series, which shows

practically the same changes in the cartilage as Case VIII, the marrow spaces in the diaphysis are excessive in size and number. The whole bone consequently presents a porous appearance. Kaufmann concludes that this is not due to lack of activity of the osteoblasts but to increased absorption of bone by osteoclasts which are seen in large numbers on the surface of bony trabeculae and calcified ground substance. Hence, although he recognises the presence of osteoporosis added to the typical appearances of chondrodystrophia hyperplastica, he distinguishes the case sharply from those instances of anosteoplasia described as osteogenesis imperfecta, osteopsathyrosis, etc.

To sum up:- The outstanding microscopical differences between the hyperplastic type and the group described first is the tendency to general overgrowth of the cartilage added to an even more complete absence of the normal changes preparatory to ossification in that tissue.

The Internal Organs in the Hypoplastic Form.

In Kaufmann's series of 13 cases, of which some were premature and all dead-born, one is struck with the number of abnormalities which are not directly connected with the disease under consideration.

Case V[1] has been mentioned once or twice as showing

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(1) Bibl.43. pg.7.

morbid features which stamp it as something more than an ordinary case of achondroplasia. Apart from hare-lip and polydactyly in both hands and feet, the subject had cystic kidneys, a cystic pancreas and a septum completely bisecting the uterine cavity.

Case IX(1) had a large sacral tumour and an unique condition of the uterus and vagina which need not be described here but which Kaufmann calls congenital hydrocolpos and hydrometra. Cases X(1) and XII(1) show "cyst formation" in the lungs. These cavities were in no way connected with the bronchioles and were purely interstitial. Apart from this, Case X had a deep groove in the soft tissues of the face which, beginning at the level of the root of the nose, ran horizontally round both sides.of the face and the ears, causing a gutter-shaped depression in the auricles which could accomodate a finger.

Virchow(2) also mentions a case with cavities in the lungs similar to those in Cases X and XII, and calls them lymphangiectatic in nature. This foetus also had a cavity in the thymus. Emerson(3) enumerates hypospadias, cervical cysts, spina bifida, defects of the auricles, defective development of the ensiform cartilage, umbilical and inguinal hernia, cleft palate, genu valgum and various neoplasms as having complicated achondro-

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(1) Bibl.43.pg.20,21,23.
(2) Bibl.27A. pg.982 loc.cit.
(3) Bibl.82.pg.683.loc.cit.

plasia, while Porak and Durante[1] add congenital dislocation of both hips, congenital adenoids, enlarged uterus, enlarged thyroid and multiple cystic disease of the kidney to this list. They also describe "congestion, recent haemorrhages and small celled infiltration in the spinal cord, liver, muscles and kidneys", and consider that this favours the view that infection rather than auto-intoxication is the ultimate cause of achondroplasia. One feels inclined to consider these findings as an accidental complication, probably of an infectious nature independent of bone disease.

But from the above enumerations one cannot but take the view that congenital morbid conditions other than the usual deformities are so common, that there is something more than simple coincidence at work, and even if we disregard the common defects in the list quoted, the frequency of cystic conditions in various organs, thyroid defects and neoplasms almost force us to suspect a general tendency to malformations and abnormal development of the tissues other than cartilage.

Jansen[2], who propounds the fascinating and, if not altogether convincing, at least very suggestive theory that pressure on the early embryo is the cause of achondroplasia, asks - "Could a rapid diminution of "the quantity of blood (caused by a rapid rise in the

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(1) Bibl.71.pg.481
(2) Bibl.88.pg.89

"hydrostatic amnion-pressure) establish a disproportion-
"be it only a passing one - between the production and
"dissolution of the gases of katabolism, so that for a
"short time the quantity of gas produced in the tissues
"exceeded that which can be carried off by the small
"quantity of blood?". I think that, going by what is seen in surgical emphysema, the absorption of the gases after the circulation becomes re-established could not fail to be rapid.

However, although no explanation is as yet forthcoming, the fact remains that the foetal tissues show an abnormally high degree of vulnerability.

For the rest, except a large liver, which is noticed in most cases, there is no abnormal condition of any of the thoracic or abdominal organs which is of constant occurrence.

In two of his cases (Cases I and III) Kaufmann describes an enlarged thyroid with parenchymatous overgrowth; the alveoli were line by polygonal cells and their lumen was obliterated, while no colloid material was found. He called the condition "struma vasculosa parenchymata congenita". The thyroid, if only because of the superficial resemblance between cretinism and achondroplasia in older children, is a structure which has been regarded with suspicion as a possible etiological factor, and abnormalities in the gland are thus of

importance. Keith[1] states that in the cases he examined the acini were irregular in shape and fewer in number than is usual in newly-born children. All the same, too many cases have been described in which the thyroid is expressly stated to be normal, to accept this abnormality of the thyroid as a constant feature. The same author states that in the testes the seminal tubules are ill-filled, the larger genital cells are few and the inter-tubular tissue is made up of a more reticulated tissue than is usual and contains fewer interstitial cells. The thymus does not appear to have any liability to special changes in this disease.

The pituitary gland has not been examined in a sufficiently large number of cases to justify any conclusion based on its minute appearances. Prof. Keith[2] states that in the gland of two cases he examined microscopically he found "a deficiency of the cells with large cell bodies, picked out by eosin". He adds in a note however, that another observer after examining the same did not agree that they showed any pathological change. One fact about it, however, has been established beyond doubt, and that is the constant diminution in size of pituitary fossa[3]. From this we may deduce the fact that the gland it harbours is diminished in size as well.

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(1) Bibl.94.pg.196
(2) Keith. Abnormal CRania,etc. Bibl.94.pg.196.
(3) Bibl.88. pg.44.

Prof. Keith[1] in an earlier article on progeria and ateleiosis and referring to the former condition said:-

".....it might be suspected that the slight reduct-
"ion in the size of the pituitary fossa is due to the
"general arrest of the cranial base. In achondroplasia
"the cranial base is arrested in its growth and the pit-
"uitary fossa is small. I do not think that a reduct-
"ion in the size of the pituitary can be explained in
"this manner. We have seen that the brain obtained by
"its growth the expansion of skull it required for its
"accomodation. In cases of acromegaly we see pituitary
"tumours expanding the pituitary fossa to a large size;
"we have no reason to think that in progeria and achon-
"droplasia the growing pituitary would fail to obtain
"such space as it required. The mere fact that bony
"processes became developed in the roof of the pituitary
"fossa seems to show that there was no energy of growth
"in the pituitary, no tendency to expansion". With this I am in entire agreement and we may conclude then that, although there is no conclusive evidence of the histolo-gical abnormality of the pituitary, we may take it for granted that there is some abnormality, if only a simple smallness. This is one of the few changes which are constant in all cases of achondroplasia.

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(1) Bibl.92.pg.308.

Where such divergence exists in the findings, both macroscopically and microscopically, in individual cases of the same group, one is inclined to ask whether the minute appearances described (on page 47) as typical of the hyperplastic variety, justify the classing of similar cases together as a definite morbid entity.

If the differences were histological only, one might be inclined to answer this in the negative and look upon the hyperplastic form as a variety differing from the classical type in degree only. Another argument in favour of regarding the second type simply as a very advanced instance of the common form is that Kaufmann's grouping together of Cases VI, VII and VIII of his series, which he considers to be instances of the hyperplastic form and which led him to describe them as a special variety, was more or less accidental and is based, apart from the softness of the cartilages, on the general flattening of the profile, as contrasted with the usual depression at the root of the nose only(1). In the skulls of the subjects mentioned a persistence of the intersphenoidal and spheno-occipital synchondroses was observed along with a normal or nearly normal sphenoidal angle. Now, as Jansen pointed out and as has been mentioned earlier in this Thesis, this general

(1) Bibl. 43i pg.31.

flattening is mainly due to a shortening with bending of the hard palate and a diminution in size, in fact almost an obliteration of the naso-pharynx. As a matter of fact the histological observations in the second group are almost entirely made in sections of Case VIII and microscopically VI and VII show practically nothing but a very marked softening of cartilage to distinguish them from the first group.

Real hyperplasia is not specially noted. This softening and porosity of the cartilaginous matrix is the characteristic element of a different group of cases, named Chondrodystrophia Malacica by Kaufmann(1), and Micromelia Chondromalacica by Kirchberg and Marchand(2). Now this pure chondromalacic element is often present in cases showing no hyperplasia whatever, as in the frequently mentioned Case V, in connection with which the author himself mentions that in his opinion the general softening and oedema of the cartilaginous tissue may be quite well explained as a result of the cystic condition of the kidneys. Softening by itself can therefore not be made the basis of creating a third variety and therefore there seems good reason for not including Cases VI and VII under this heading. But the best proof that general flattening of the face has no connection per se with hyperplasia or softness of the cartilage in the basis

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(1) Bibl.43. pg. 60
(2) Bibl.39.

cranii is that in the last case of the series, No.XIII, which is described as a most beautiful example of hyperplastic chondrodystrophy and which showed the generally flattened profile to perfection, there was no persistence of cartilage in the tribasilar bone. In connection with this Kaufmann remarks - "it was surprising however, to find a partial, densely hard synostosis of the os tribasilare and a vertical position of the same"(1). With this the justification for classing Cases VI,VII VII together disappears altogether. Does this then imply that there are no valid grounds for recognising the existence of a second variety of chondrodystrophy? We venture to think it does not.

Quite apart from the histological appearances which show a true hyperplasia, there are features in Cases VIII and XIII of Kaufmann's series which distinguish them from ordinary achondroplasia. A similar case has been described by Dr. Ballantyne in the Manual of Ante-natal Pathology(2) as an example of what the author called "Type C." of foetal bone disease. He points out the similarity between this foetus and the two-mentioned. A fourth case is that of James R. to be described below. I have found no other similar cases in the literature but these four resemble one another so closely and are

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(1) Bibl.43. pg. 61
(2) Ballantyne. Manual of Ante-natal Pathology.Bibl.84.

so easily and definitely distinguished from the commoner form of the disease that one is justified in classing them together as a special variety and as even macroscopically the marked enlargement of the epiphysis is the outstanding feature, so much so that it may dominate the whole clinical picture, we may as well continue to describe the condition as chondrodystrophia foetalis hyperplastica, remembering however, that it is only a modification of the better known form of chondrodystrophy usually named achondroplasia.

Before I give the notes on the case of James R. I must express my regret that they are not more complete. Unfortunately when the baby was brought up to the Out-Patient Department, the deformity of the limbs dominated the picture to such an extent, that none of the several members of the surgical and medical staff who saw the patient were struck with the disproportion in size between the trunk and limbs and its connection with the typical cases of achondroplasia, was not at first suspected. Accurate measurements therefore are lacking at this stage. The existence of spinal deformity is not commented upon in the notes then. From the skiagrams taken a few days after the child was first seen we find that some disproportion between the length of the trunk and that of the limbs actually did exist but there cannot have been anything like as marked a discrepancy between

them as was noted later. One simply could not have missed it when the skigrams were taken. The same holds in the case of the chest deformities.

After the skiagram had revealed the nature of the condition, the patient was not seen again for several months, after which he was admitted to the Wards.

The most unfortunate part, however, was that after the child had been under constant observation for 6 or 7 months and shortly after I had left the Hospital, he was discharged. Early in June he is said to have been taken ill. Measles was diagnosed and the child sent to a Hospital for infectious diseases. The diagnosis was not confirmed but the day after admission he died. He was then 14 months old. The cause of death was notified as acute broncho-pneumonia, but no autopsy took place. I only heard of this a fortnight later. It is interesting to note that when this news was conveyed to me by the mother, she told me that she had recently given birth to a perfectly normal baby. For the reasons mentioned the observations are not of as much value as I should have liked them to be, but yet I think that, incomplete though the record is, publication is justified because of its rarity and the instructive nature of the skiagrams.

Case of James R. aet 21 days. Admitted as out-patient under the care of Mr. R.C.Dun, on May 8th,1912.

Previous History. The child is the result of a fourth pregnancy which was normal. The mother declares that she was unable, through poverty, to obtain sufficient and proper food. At the confinement she was attended by a midwife. The presentation was pelvic but she states that labour had been fairly easy. It was followed by a normal puerperium. No details about the secundines could be obtained. The baby was puny and obviously deformed but took the breast well.

Family and surroundings. Father a healthy dock labourer aet 33. Mother a somewhat pale, but apparently healthy woman aet 29. She has been pregnant 3 times before and in each case gave birth at full term to a healthy child. No miscarriages and no suggestion of early abortion or attempt at procuring this.

There is no trace or hint of lues, congenital or acquired, in either parent. The father is a moderate drinker, the mother an abstainer. The first child died aet 3 years of measles and broncho-pneumonia. The second died when 9 months old, of "concussion after a fall". The third is now 2 years old, alive and healthy. The home is a poor one, the father having been out of work for several months. The baby has been breast-fed since birth.

Present Condition. The child is small and thin and weighs 5 lbs.9 oz. He moves the limbs to some extent and cries feebly. There is a striking deformity of both upper and lower limbs, chiefly the latter. The attention is at once arrested by the appearance of the knees which are very large. This enlargement feels very hard, no fluid can be made out. About 1½" below the line of the joint the limb narrows very suddenly, causing a hard, sharp irregular edge. In front this is rendered even more prominent by a hard spinous outgrowth. At the junction of the wide and the narrow part there is a sudden bend inwards of the leg producing an angle of about 130°. The knee itself is flexed and cannot be extended beyond an angle of about 140°. Flexion is less interfered with but is not complete. Some coarse "cartilaginous" grating is felt when passive movements are made but these do not seem to cause the baby any pain The narrowed part of the leg is very short and ends inferiorly in another wide expansion. At this junction outward angulation is seen. The foot is long and narrow and presents the appearance of pes planus with valgus deformity, and these two features, added to the increased length of the foot, produce an appearance reminiscent of a deformed adult foot rather than of a talipes valgus in a young baby. Slight thickening is noticed round the phalangeal joints which are somewhat difficult to move.

Above the knee the thigh shows the same dumb-bell appearance, also obviously due to a great disproportion in the circumference of the very large epiphyseal ends and the thin and short diaphysis. The great trochanter is extremely prominent. No spinus process, like that seen in the tibia, is noticed. The hip joint has a small range of passive movements; the same sensation of muffled grating is transmitted to the hand as in moving the knee. The movements are limited in an equal degree in all directions.

The upper extremity shows the same type of deformity as that seen in the lower limb but to a less extreme degree. Here also one is struck with the tremendous size of all epiphyses as compared to the very short and thin diaphyses. Especially the head of the humerus is huge. The carpus is very large and broad. The fingers are long and tapering and of unequal length and here also one notices the resemblance to an adult hand. Passive movements are limited, especially abduction at the shoulder and extension at the elbow.

All these changes in the limbs are absolutely symmetrical. There is no craniotabes. The fontanelle is fairly large and the tension is normal. There is no facial irritability.

The clavicles are well formed. The trochanters give the pelvis a broad appearance.

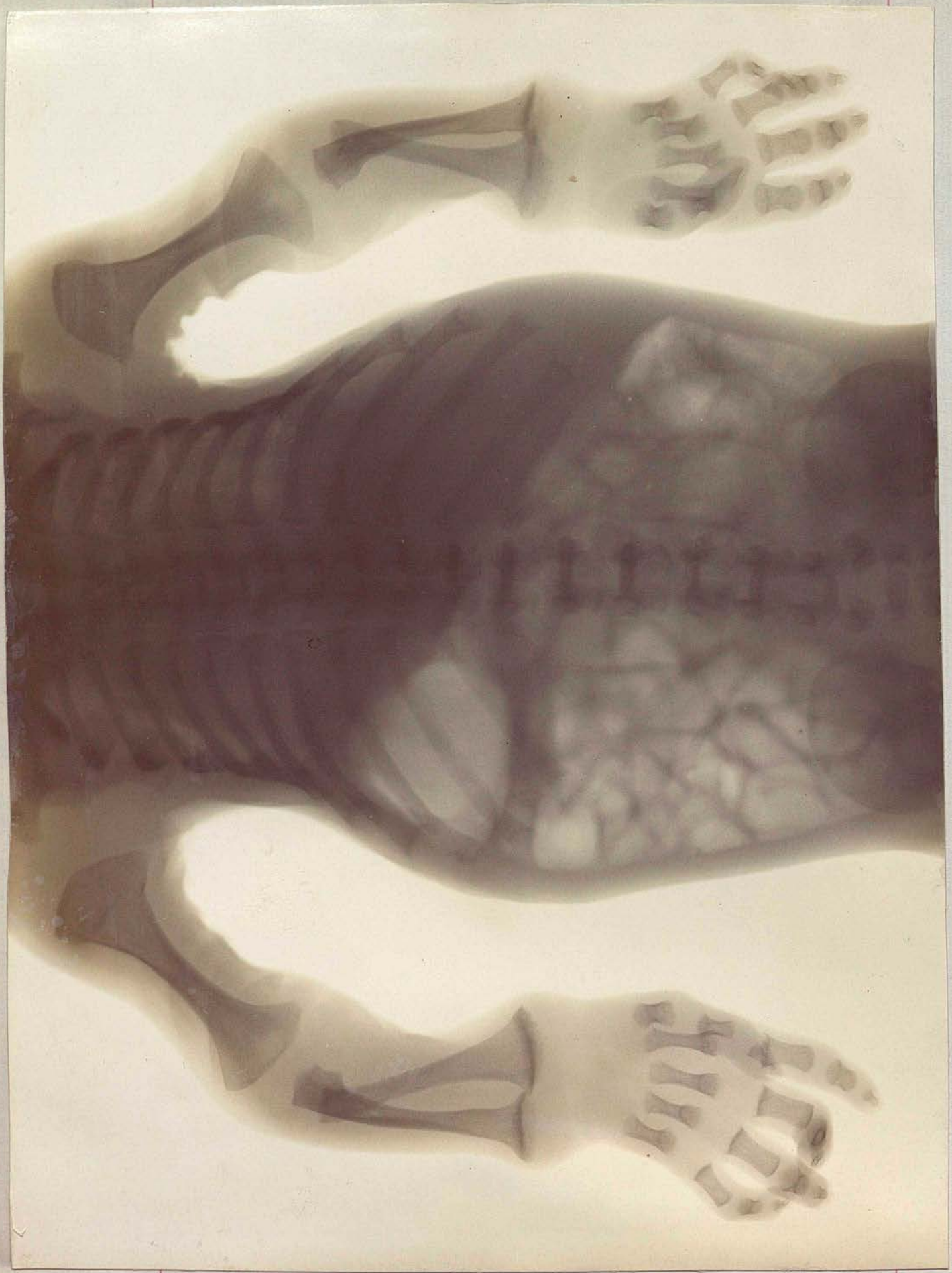

PLATE 7.

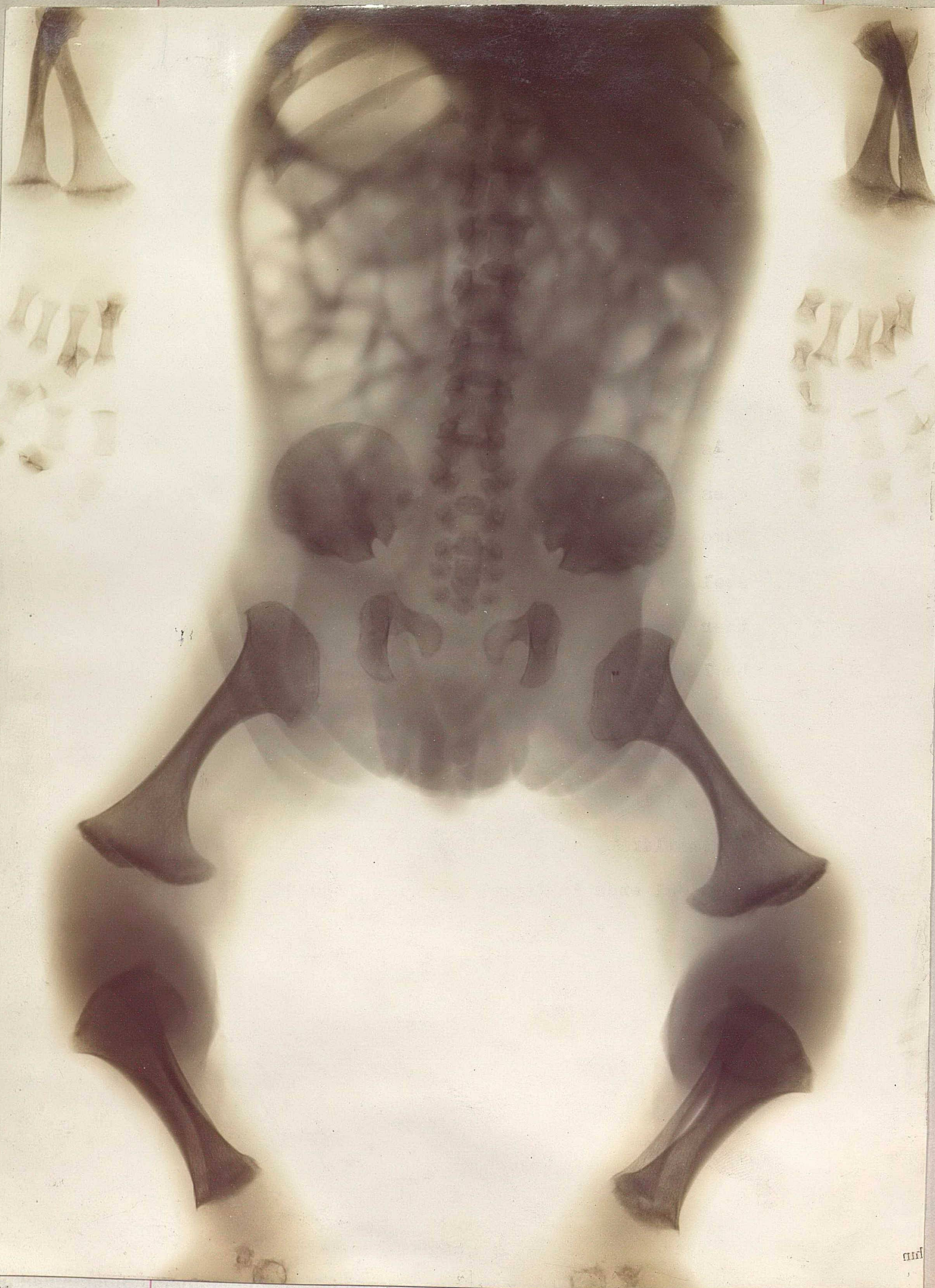

Plate 8

was made of a palpable rosary. The bones are very transparent and ossification is backward. The backwardness in development of the lower dorsal and lumbar vertebrae and the sacrum as compared with the upper dorsal ones is obvious. The hands show a picture altogether different from that seen in Plate 3.

It also cannot escape notice that such a large part of the skeleton of the extremities is made up of cartilage. As a result of this the total length of the limbs does not suffer as much as the short diaphyses would have caused in the absence of the tremendous epiphyseal overgrowth. In fact, if we put Plates 6 and 7 together in the proper manner and remember the fact that the limbs could not be straightened and as a result show an apparent shortening in the skiagram, only a moderate degree of disproportion between the length of the trunk and that of the limbs is observed.

The similarity in the nature of the appearances at the diaphyseal ends in these plates and those in Plate 2 is very marked. In the latter we have this same cupping with bony overgrowth at the junction of epiphysis and diaphysis although in a much lesser degree. Here also the backward ossification (the baby is 11 months old) and the transparency of the bone is obvious.

A peculiar ragged appearance is presented by the upper end of the diaphysis of the tibia at the area for ossification of the anterior tubercle in Plate 2, which

is a skiagram of Dorothy P.'s legs. The same is seen in Fig.21 in Jansen's book, on page 24. The X-ray plates shown in his work show the same type of changes as the ones noted in those published here.

The soft tissues in JamesnR's plates, however, show nothing of the marked overgrowth seen in typical cases.

Let us now come back to the notes on James R's case.

Between May 14th and Aug.21st the child was not seen by me. On the latter date however, he was brought up again suffering from diarrhoea and was admitted to the Hospital. The following notes were made:-

21.8.12. The child looks very weak, miserable and badly nourished. Temp.98.4.Pulse 122. Respiration 32. Weight 7 lbs. Length 21".

The child looks very peculiar. The head is large and square, occiput flat and the whole head markedly brachycephalic. Greatest circumference 16 1/8". The anterior fontanelle cannot be accurately measured as the coronal, sagittal and metopic suture open out gradually towards it. The lateral fontanelles show depressions, but it cannot be definitely made out whether they are still open. The anterior fontanelle is sunken. The forehead is somewhat square and the root of the nose slightly depressed. The palate is well formed and more arched at the back than in front.

The eyes are normal in shape and the orbital fissures lie in the same straight line. The pupils are equal and normal in size. There is no facial irritability.

The trunk is large in proportion to the limbs. Distance from crown of head to umbilicus 11½".

The chest is narrow above and expands badly with respiration. Circumference at level of nipple 12¾" and at the lowest level of the 10th costal cartilage 15¼". There is a marked bulging forward of the

sternum and costal cartilages and a well developed Harris' sulcus. The thoracic cavity shows a tendency to expand towards the outlet.

The spine shows a combination of scoliosis and kyphosis. The latter is most marked at the level of the 9th dorsal vertebra while the lateral deformity attains its maximum at the 7th dorsal spine. The convexity is towards the right and a compensatory lateral curve with the maximum bend at the level of the 2nd lumbar spine is present. Both antero-posterior and lateral movements are limited. These curvatures do not disappear on suspending the child from the axillae. The shape of the chest shows the usual scoliotic deformity.

The clavicles have the normal curves exaggerated but do not show deformities comparable to the other long bones.

The abdomen is distended. Circumference at the level of the umbilicus 14".

The pelvis seems narrow. The distance between the anterior superior spines is 3½" and between the great trochanters 4 3/8". The coccyx is very easily palpable and seems enlarged with a marked forward curve.

The appearances of the limbs are identical with those noted before. The distance from the acromion to the tip of the middle finger measures 7". That from the anterior superior spine to the plantar surface of the heel 8¼". The hands and feet are elongated and the digits taper towards their distal extremity.

Respiratory system. The child has a snuffling and noisy respiration. No nasal discharge. Frequent bouts of coughing. Percussion shows emphysema and collapse in parts conforming to the chest deformities. On auscultation rhonchi in various places and some medium crepitations at the bases are heard.

Circulatory system. There is no superficial cardiac dulness. The heart sounds are weak but no murmurs are heard.

Alimentary system. The tongue is furred and moist Abdomen distended with flatus. Stools are passed 8 or 9 times in 24 hours, the faeces are offensive, watery and green.

The upper border of liver dulness cannot be made out with certainty owing to emphysema of the overlying lung substance. The lower edge is felt ¾" below the costal margin in the nipple line.

PLATE 9.

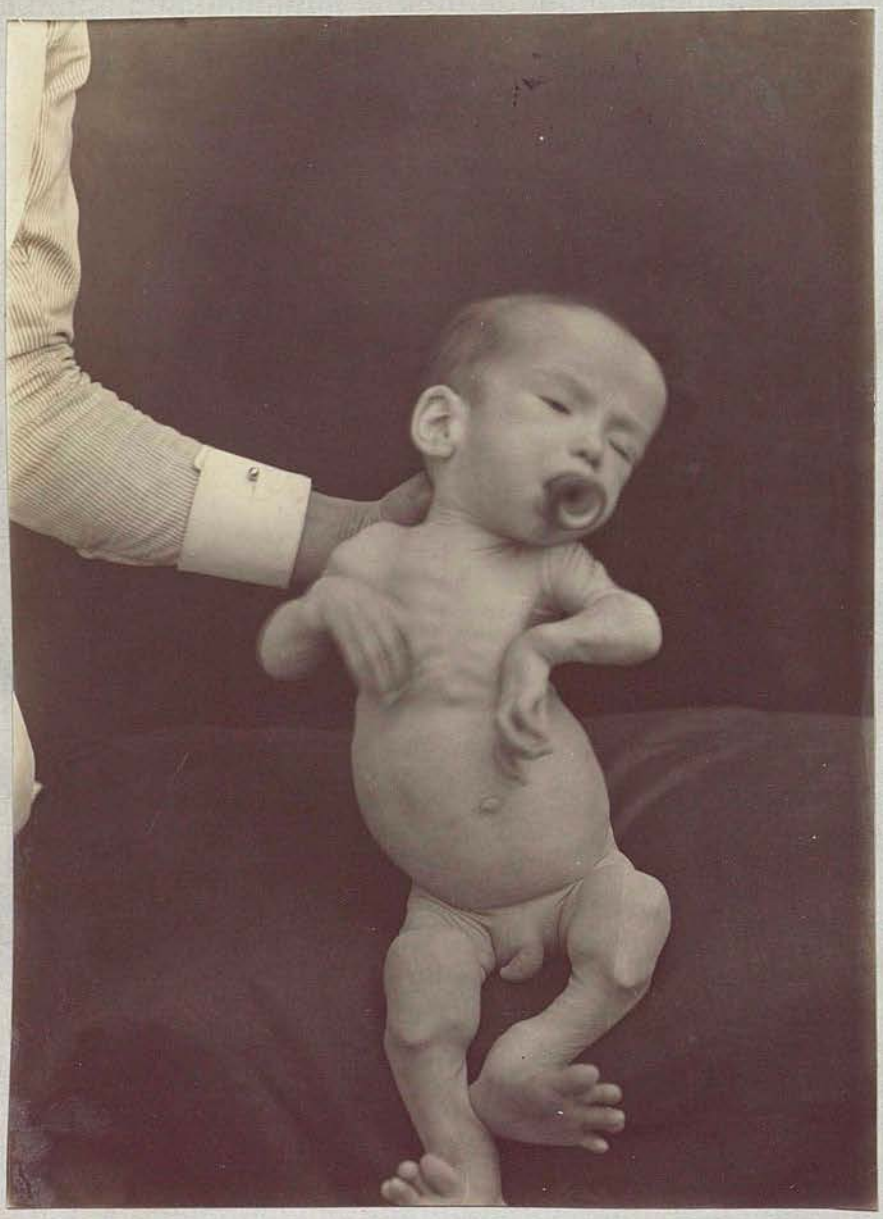

PLATE 10.

Genito-urinary system. The testicles lie in the upper part of the scrotum. The penis is large and there are some preputial adhesions.

Glandular system. No enlarged lymphatic glands are felt. The spleen is not palpable. The tracheal rings are easily felt and no enlargement of the thymus can be made out.

Nervous system. No facial irritability, laryngismus or fits. Baby sleeps fairly well.

It seems hardly necessary to copy here the copious progress-notes which refer entirely to the respiratory and intestinal condition for which the child was then treated. After the first few days when the diarrhoea had been got under control the mother came up to the Hospital three times a day to feed the child. The breast feeds were supplemented by Glaxo, 3 drachms to 3 oz. of water.

The cough became very troublesome and on Aug.26th 1912, 5 days after admission, respiration stopped suddenly after a fit of coughing. The child became cyanosed and the radial pulse could not be felt. The throat was cleared, artificial respiration started at once and 10 minims of ether given intramuscularly. This revived the patient and after that slow improvement took place.

On Aug.29th the photographs shown in Plates 9 and 10 were taken. The deformity of the knees is well shown in Fig.10, where the spinous projections are very evident. This also shows the hands which are so completely different from those seen in typical achondro-

plasia. Fig. 9, though a bad photograph, may be used to show the kyphosis described while the fact that ex-suspension does not straighten the spine is also brought out. Again, this shows the moderate degree of shortening of the legs if one remembers their flexed position. The large coccyx also shows well.

During all the time the child was in Hospital (from 21st August 1912 till 30th March 1913) the weight only increased from 7lbs to 9lbs 11oz. He gained pretty steadily during some periods while sometimes the weight remained about the same level for several weeks with temporary drops and recoveries. At first the temperature fluctuated and might show a rise, either in the morning or evening but this did not exceed 99° except on one occasion. This was between the 11th and 16th of September when continuous pyrexia, reaching a maximum of 100° on the 15th occurred. During that time the notes show that the patient was not quite so well. He passed a few loose stools containing an excess of fat. Citrated and diluted cow's milk was then substituted for "Glaxo" but the breast feeds were continued till 12th October when the mother declared that the milk gave out. The child was then 6 months old.

On the 16th of September, at the end of the short pyrexic period mentioned above, when the temperature had come down to 98.4 the fontanelle was found to be

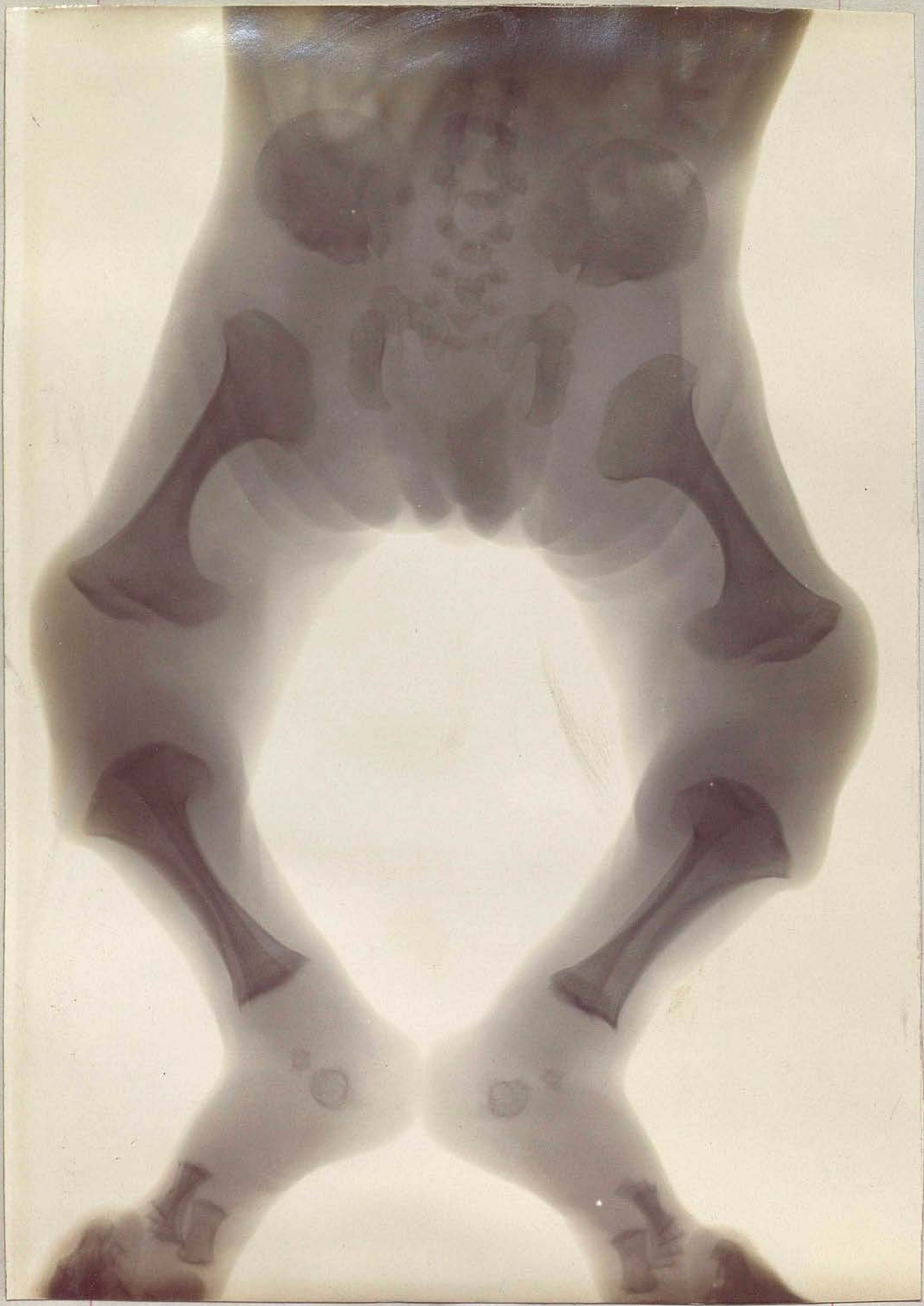

PLATE 11.

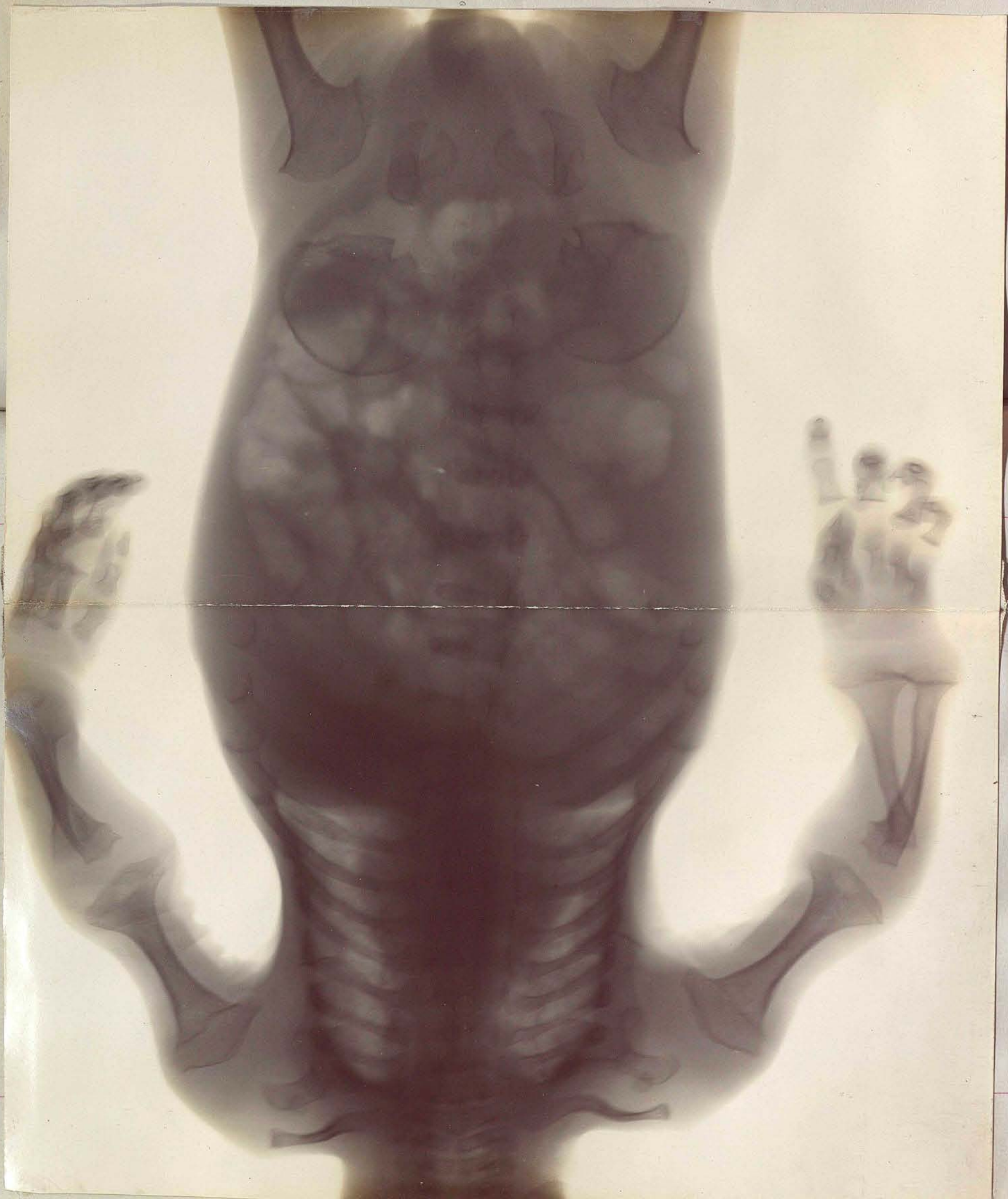

PLATE 12

PLATE 13.

tense, while the veins of the scalp and forehead were noted to be full. On the next day the following entry is made in the notes:- "Temp.97. Resp. 52. Pulse 148. "Patient looks about the same as in the early morning. "Fontanelle not quite so tense. No head retraction. "Veins still prominent". Curiously enough he gained two ounces that day.

The fulness of the superficial veins of the forehead along with a somewhat increased tension of the fontanelle persisted when James left the Hospital.

Apart from the treatment indicated by the condition of the lungs and alimentary canal, thyroid extract was given from 28th August till 12 October, beginning with 1/6gr.b.i.d. and increased to 1/4gr. b.i.d. but without any effect.

On 5th October a second series of skiagrams was taken, including one of the head which is shown in Plate 6. Mention of the head has already been made while discussing the cranial deformities (page 22).

Plates 11 and 12 show the skeleton at the age of 5½ months. There is an interval between this series and the first of 4½ months and yet there is hardly any progress visible. The lower epiphysis of the femur still shows no attempt at ossification. The ossific centres in the os calcis, just included in Plate 7 are still about the same size. The only progress visible after careful comparison seems to be that the deficient

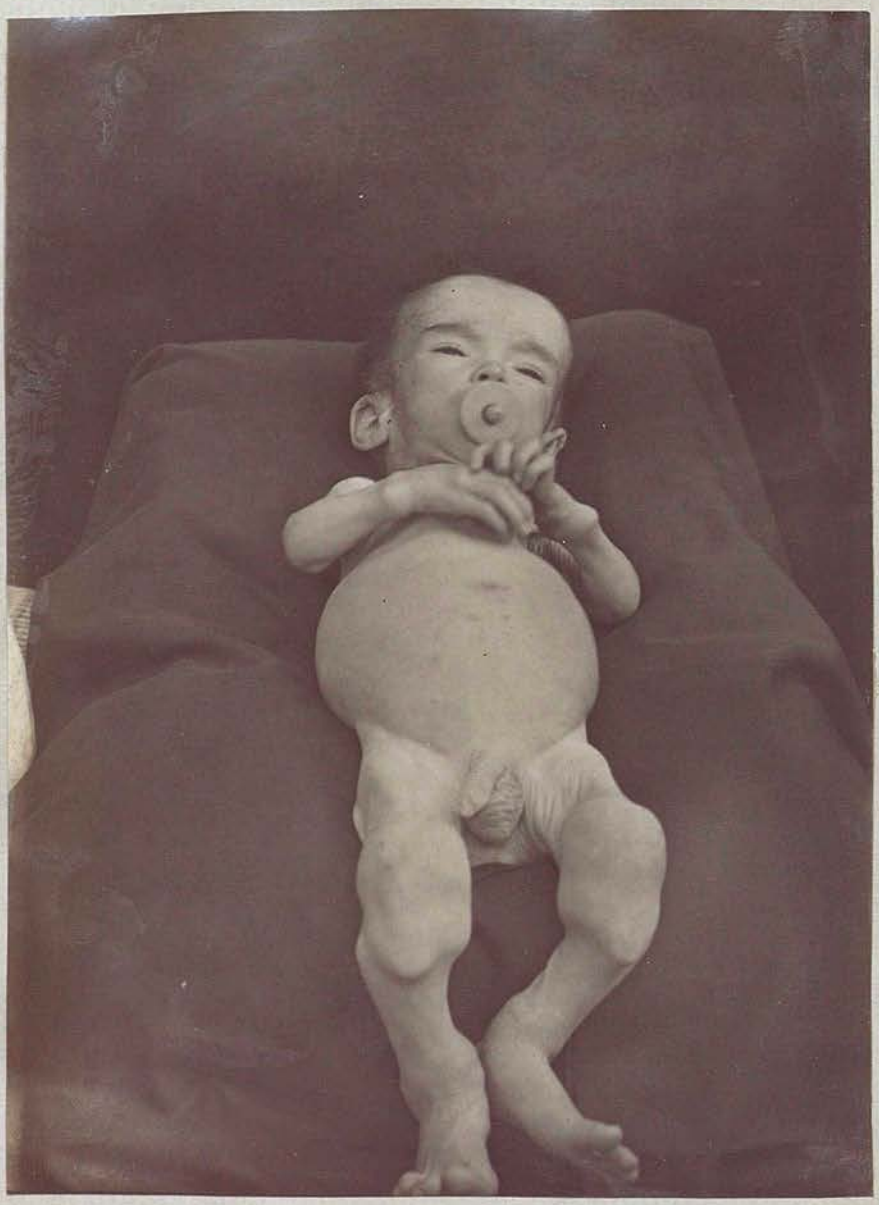

PLATE 14.

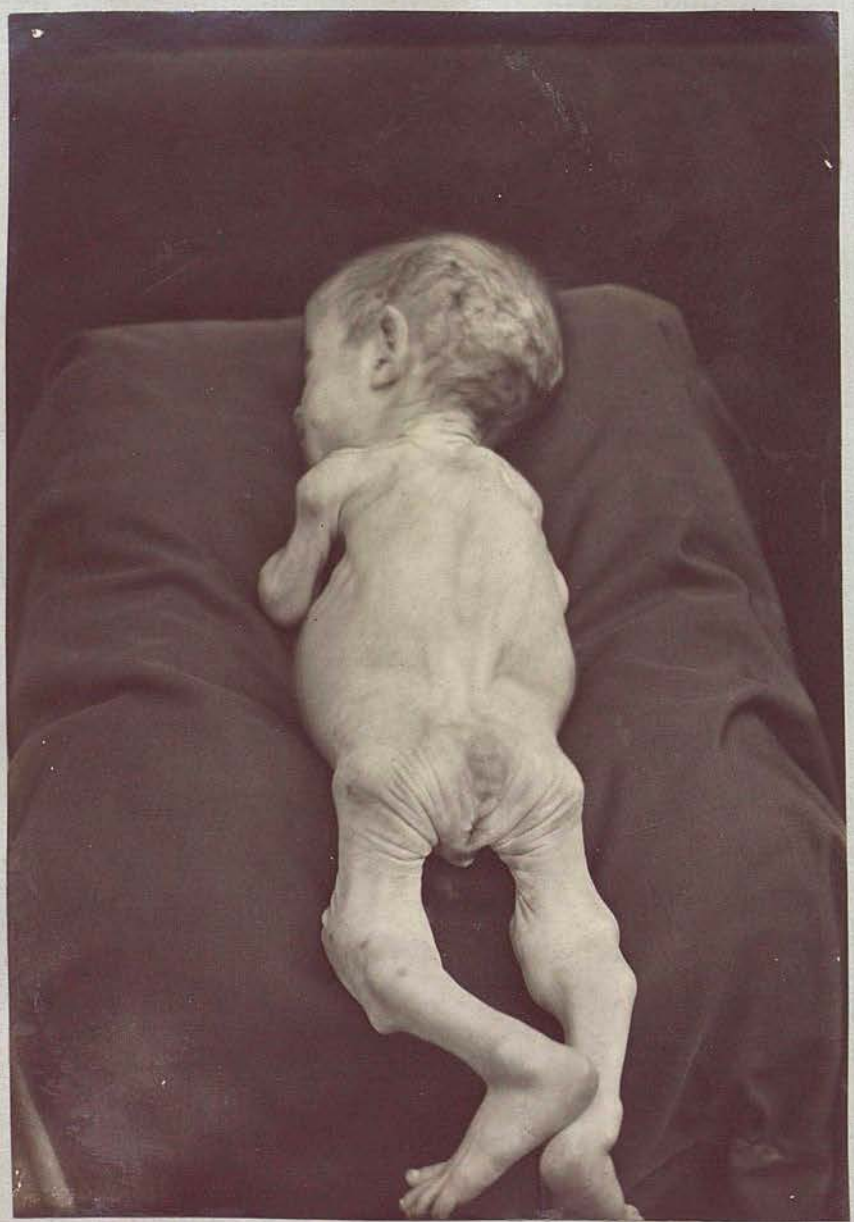

PLATE 15.

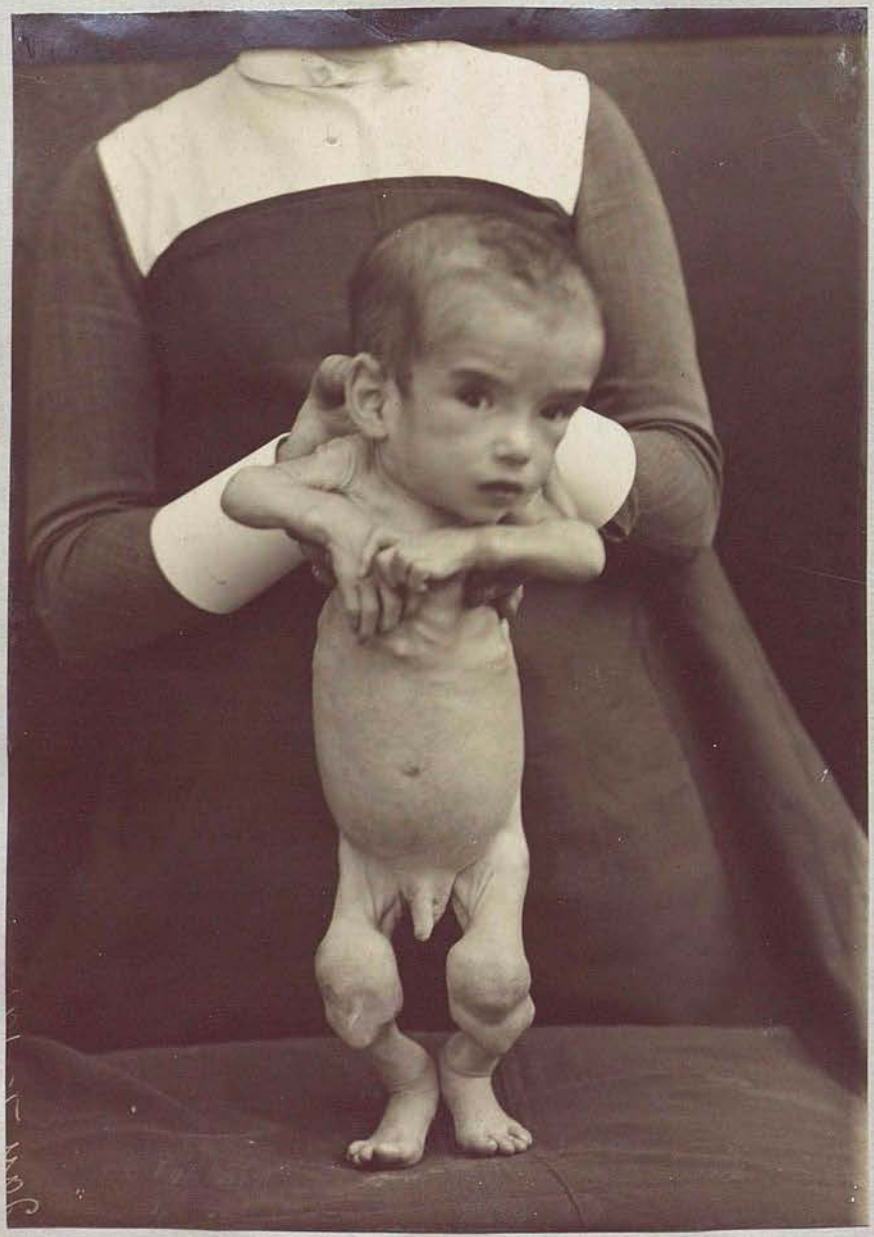

PLATE 16.

PLATE 17.

ossification in the first piece of the sacrum, seen in Plates 7 and 8, shows some slight improvement in the later skiagrams.

On the same day the photograph shown in Plate 13 was taken.

For several more months the patient remained under observation. No teeth ever appeared. The child's intelligence seemed to be normal but he never made the slightest attempt to sit up; he could not even hold the head up. All the time he was in Hospital he had constantly recurring attacks of slight diarrhoea and some bronchial trouble without, however, a definite rise of temperature.

On 7th January a fresh series of photographs was taken shown in Plates 14-17. No.14 shows the appearance of the limbs at that time. No.15 gives some idea of the shape of the back, the large coccyx, the prominence of the head of the humerus and the general thinness of the patient. At that time he was as well as ever and weighed 9lbs. 4oz, which was more than it had ever been. Plates 16 and 17 show that by now he has acquired the typical achondroplastic facies, not the generally flattened profile, Kaufmann emphasizes in his cases, and how much more he resembles the common form, but also where he differs: in the general lack of subcutaneous fat, in the extraordinary condition of all the epiphyses and in the chest deformity and, last but not least, in the shape of the hands and feet. The side view in Fig.17 shows

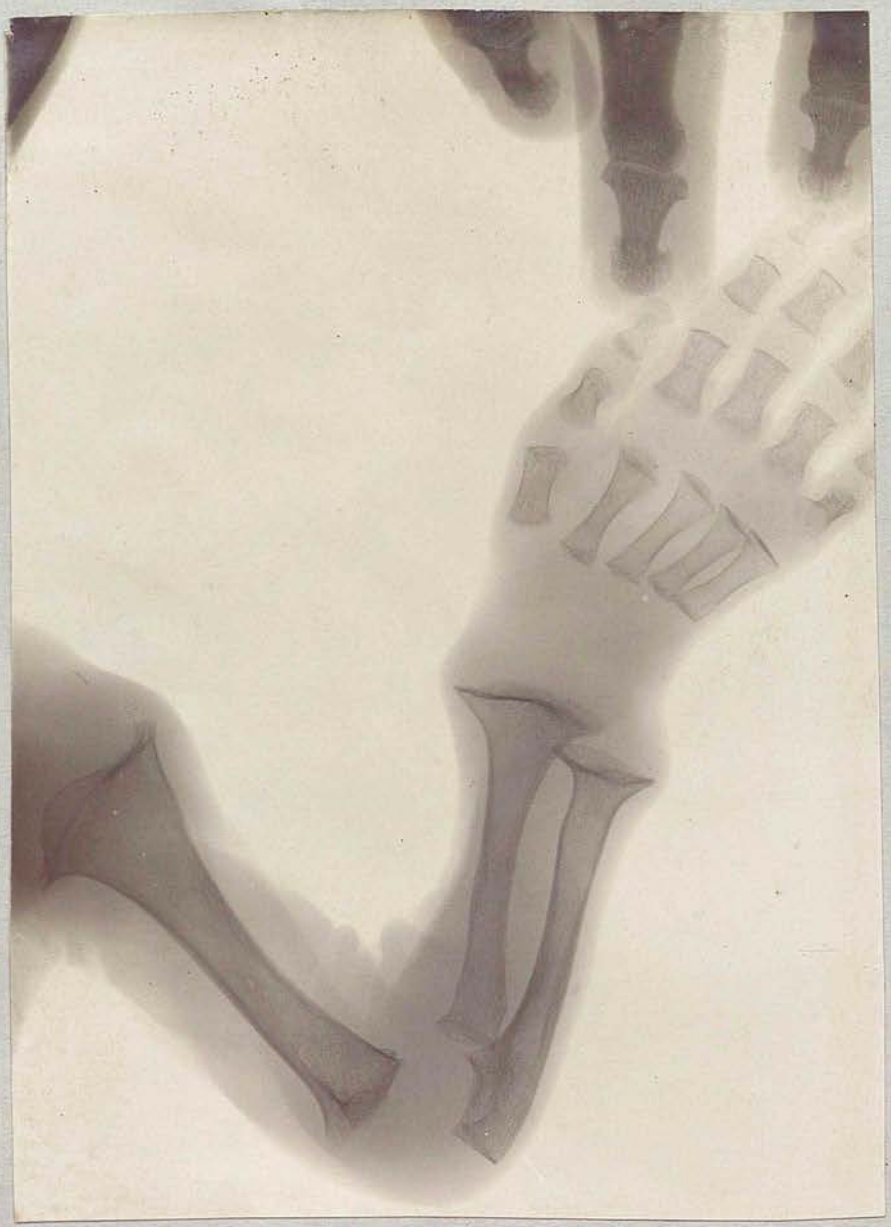

PLATE 18.

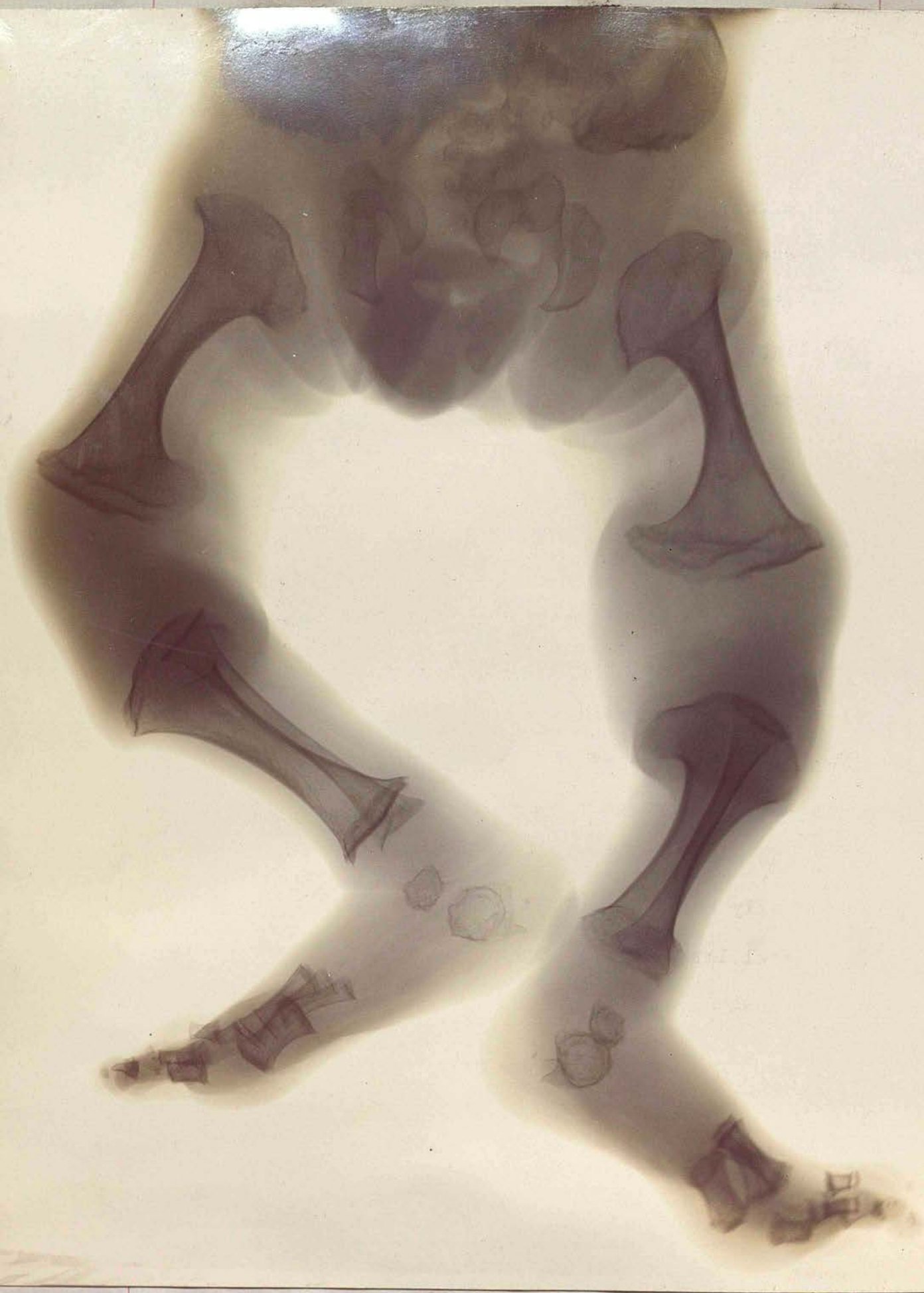

PLATE 19.

Plates 18 and 19 show the radiographic appearances at the same time. The former should be compared with No.3 showing the hand of Dorothy P. when 13 months old to illustrate the similarity in the diaphyses and the difference in the hands.

Plate 17 shows two changes from Plate 8, viz. a very slight advance in the ossification of the os calcis and a very slight lengthening of the diaphysis of the fibula as compared to that of the tibia which, as mentioned before, is commonly noted in the ordinary form of achondroplasia.

Now even without measurements of the child when he first came under observation, there can be no doubt that when he was just over 11 months old the resemblance of this case to one of typical achondroplasia was very much greater than was noticed shortly after birth. Since the measurements on August 28th there had been practically no growth of the lower limbs and the increase in general length, though only amounting to $1\frac{3}{8}$" in 7 months must have been due to the head, neck and trunk only. Then when studying the face in the different photographs it can be seen to assume the "cretinoid" type more and more.

A complicating element in the case is the occurrence of the chest and spinal deformities, the constantly recurring attacks of catarrh of the bronchial and

intestinal mucous membranes, the absence of any sign of beginning dentition and the backward state of the fontanelles. Of course rickets suggests itself at once as an explanation for this symptom complex.

It must be remembered however, that the child was wholly or partly breast fed until he was 6 months old. The added food was Glaxo at first and though this has been reported to have caused scurvy in some isolated cases, I do not know of any instance where rickets could be traced to it. But apart from this and granting that, theoretically, rickets may occur even in children fed like James R., would it not be very surprising if in a case of rickets acquired at such an early age and manifesting itself in the degree of severity necessary to produce the changes described, there had been no nervous symptoms? In however delicate and ailing a condition the child was, he never at any time had convulsions, laryngismus, Chvostek's sign or any of the numerous nervous disturbances so inseparable from rickets in young babies. But if the reason why in my opinion the complication cannot have been the result of acquired rickets do not seem as conclusive to others as they appear to me, there can be no doubt whatever that the main deformities are entirely different from those seen in rickets and that even if one could admit the theoretical possibility of intra-uterine rickets,

a mere glance at the earliest skiagrams would be sufficient to show that the disease from which our patient suffered was achondroplasia and nothing else.

There is also the suggestion of some interference with the circulation of the cerebro-spinal fluid: somewhat enlarged veins and a slight increase in the tension of the fontanelle with a large head. This never proceeded far enough to label it a definitely established hydrocephalus. One has only to glance at Plates 14 and 15 to see that the shape of the head does not suggest that condition as the main cause of its abnormal appearance. Curiously enough a certain degree of hydrocephalus is a not uncommon occurrence of achondroplasia; e.g. it occurs twice in Jansen's five cases. In this condition it may have been a complication or it may have been a somewhat unusual symptom of the disease. We must refer to Jansen's opinion that excessive pressure to which the embryonic head is subjected and which is due to an abnormally high intra-amniotic tension is the cause of the deformities in the skull and brain and that "the compression of the basal part of the brain in the "achondroplastic foetus.....may easily lead to a "narrowing and an obstruction of the vessels behind the "3rd ventricle and may thus account for the relatively "high frequency of hydrocephalus in this disease". We cannot decide however, whether in James R's case

(1) Bibl. 88. pg. 87-88.

the fulness of the veins and tenseness of the fontanelle was in any way a result of his disease.

It has been assumed by almost all observers that chondrodystrophia is a purely foetal disease and that, though the original manifestations may have imprinted their special features on the growing and full-grown skeleton, the morbid influence has ceased to act. at birth. Although being the first to admit that the case at present under consideration cannot, owing to the incompleteness of the records, be held to prove the contrary, there seems to me to be a strong probability that a post-natal factor must have been at work as well as an intra-uterine one. One might suspect that the impression of a progressive condition produced on my mind during the 10 months the child was under constant observation was due to details observed only as my acquaintance with the literature became more extensive but which had been present before. The photographs published however, point to some actual progress. But what to my mind is conclusive proof of my contention that in this case at least, the morbid process had not ceased to act at the time of birth is the fact that the skiagrams show little or no changes as the child grows older and that e.g. when the baby was eleven months old, the lower epiphysis of the femur showed the same complete absence of ossifying tissue as was observed when he was 20 days. This, surely points to something more than a purely ante-

natal interference with ossifying cartilage. By carefully comparing the skiagrams with those of normal skeletons of the same ages, many similar instances can be found. I therefore hold that, whatever else may be the rule in typical hypoplastic cases, one hesitates to assume the cessation of all morbid activity at birth in the cases of which James R. is an example.

Unfortunately again, there is no proof that the case described shows the same histological changes as the cases called hyperplastic by Kaufmann. For several reasons, however, I claim the right to class this case as hyperplastic chondrodystrophy. First of all the peculiar deformity of the limbs are due to an enlargement of the epiphyses out of all proportion to the diaphyses. This is shown by the skiagrams. Then, if one compares this subject with those in which histological proof has established the diagnosis, we find a striking similarity between them.

In his Manual of Ante-natal Pathology, Dr.Ballantyne[1] reproduces a drawing of the case representing Type C. This foetus is the exact image of James R. as he appeared when first seen, except for the greater prominence of the former's coccyx which however was less curved than my patient's. As a matter of fact it was this picture that gave me the first clue to the true nature of the condition. The description of Dr.

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(1) Bibl. 64. pg. 338.

Ballantyne's foetus tallies in every respect with what was observed in James R. and the histological findings were undoubtedly those of chondrodystrophia hyperplastica

Kaufmann's cases VIII[1] (which is that of a premature foetus only 24 c.m. long) and XIII[2] correspond in their description as well as in the drawings of the bones with the case here recorded.

Whether these three cases would have confirmed my suggestionof post-natal morbid activity must remain doubtful as none of these subjects led an independent existence, in fact it is generally held that this form of the disease is incompatible with extra-uterine life.

Leaving the histological changes out of the question we can summarise the distinguishing features of chondrodystrophia hyperplastica as follows:-

1. Great overgrowth of the epiphysis with striking variations from the normal anatomical outlines.

2. A high degree of expansion at the diaphyseal extremities to accomodate the huge epiphyses.

3. A deficiency of the subcutaneous fat, so abundantly present in ordinary achondroplasia or chondrodystrophia hypoplastica.

4. Long and thin hands and feet with tapering digits, in every respect different from the "main en trident"

5. A much lower degree of viability as well as vitality

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(1) Bibl. 43 pg. 16
(2) Bibl. 43. pg. 60

RADIOGRAPHIC APPEARANCES.

The radiographic appearances of achondroplasia have been studied by Bonchacourt(1) and Levi(2) and others in the foetus and by Cestan and Infroit(3) in older children.

In the main the findings confirm what is seen in the prepared bones. The epiphyses show large as a rule and where ossification has taken place the osseous parts are separated by large clear spaces.

The hands show the divergence of the metacarpals and their phalanges from each other, mentioned above.

Ossification has been stated to be more advanced. This is not confirmed by the skiagrams reproduced here or in Jansen's Monograph. In all these ossification is very backward. In the latter's work in Plates 18 and 21 skiagrams of an achondroplastic and a normal skeleton at the age of 5 years is shown and there this point is very obvious. The shadows of all the long bones are more transparent than in normal subjects. The pathognomonic feature of the disease as revealed by the X-rays however, is the expansion with hollowing out of the diaphyseal extremities into a cup of a wavy and irregular outline, in which the bone is seen to thin out towards the periphery. It is fouhd in a greater or lesser

(1) Bonchacourt. Radiographies. Bibl.67. pg. 58
(2) Levi & Bouchacourt. Radiographies etc. Bibl.68.pg.514
(3) Cestan & Infroit. Bibl.56. pg. 437.

degree in all achondroplastic bones but it is more obvious where there is much enlargement of the epiphysis and hence is seen best developed in cases of the hyperplastic type.

In doubtful cases, and many such are met with in young children, a skiagram will definitely clear up the diagnosis. Porak and Durante(1) gave as their opinion that clinical signs may be insufficient to come to a definite diagnosis and that the microscopical appearances may have to be studied before one can be certain

Fortunately it is not necessary now to reserve our opinion till the material necessary for this mode of investigation is available.

Before leaving this part of the subject I should like to refer specially to the collar-bone. All investogators agree in looking upon the clavicle as the long bone least affected in the subjects of the disease.

The usual abnormality is a slight shortening of the distance between the acromial and sternal ends, due to an accentuation of the normal curves. Apart from this there is usually said to be no interference with its ossification.

In Plate 12 however, the outer part of the clavicle shown is much less developed than the inner, although on palpation this was not noticed. The former half is also more transparent and some waviness in the outer bony

(1) Bibl. 71. pg. 481.

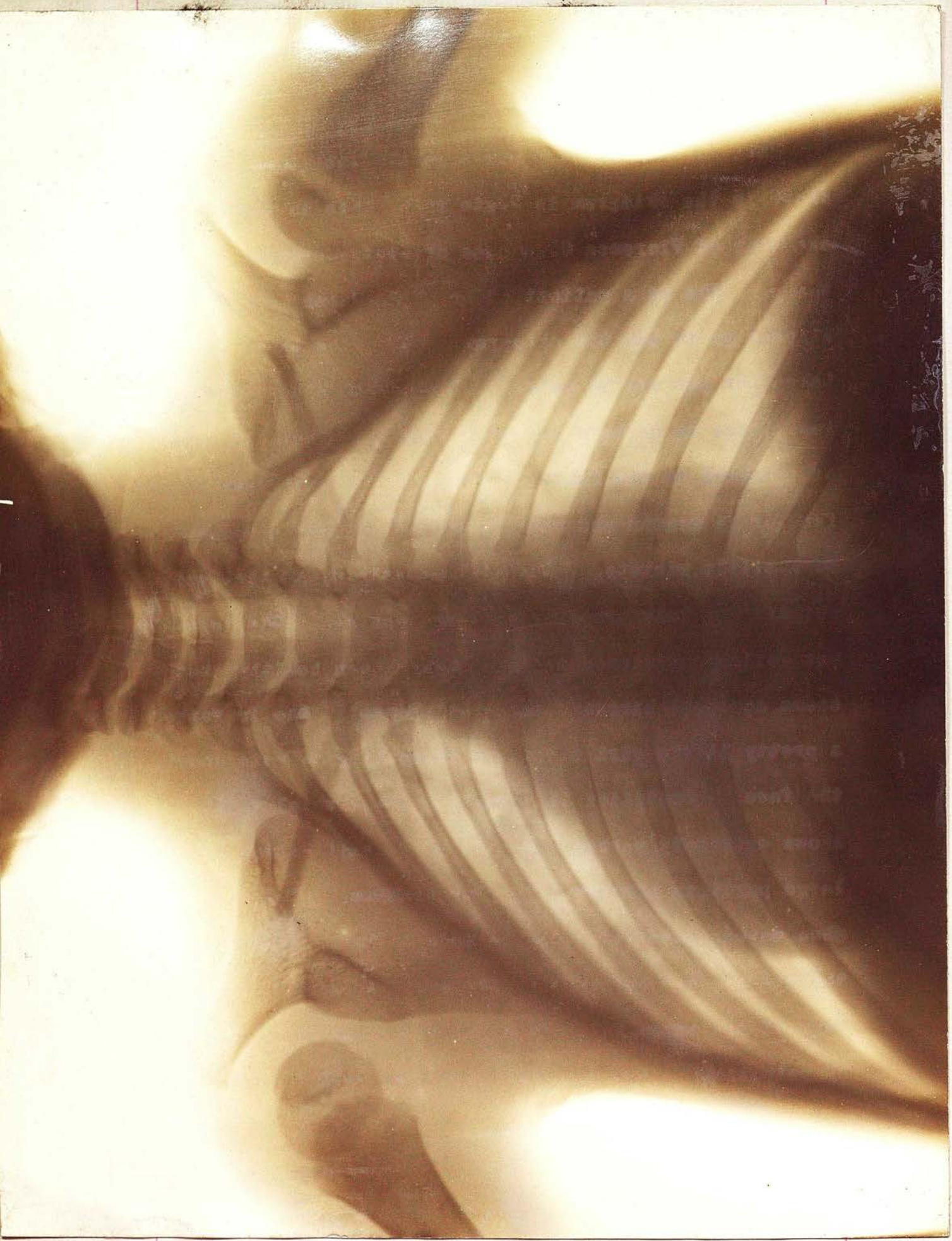

PLATE 20

extremity, with an attempt at "cup-formation", can be made out.

Let us compare this for a moment with the clavicle shown in the skiagram in Plate 20. This is part of the skeleton of Florence G. a case of cleido-cranial dysostosis. She is a patient of Dr. N.P. Marsh who kindly allowed me to use the skiagram. When the photo was taken her age was 5½ years. The points in her case of importance to us here are as follows:- There is nothing of interest in the family history. The child was breast fed for 11 months and when 14 months old was supposed to be a little rickety. She started walking at that age but did not talk properly till she was 4½. She is small but well proportioned and has always been healthy, but seems somewhat backward in intelligence. She is rather a pretty little girl and there is nothing to note about the face. Dentition is normal. The cranial vault shows extremely marked deficiency in ossification and large portions are completely membranous. The shoulders, when moved passively, can be made to touch in front of the sternum without causing her any discomfort. A rudiment of the outer half of the clavicle can be recognised by palpation. All the other bones as well as the internal organs are quite normal.

When examining Plate 20, which shows other points of interest which do not concern us here, we notice extremely

bad development of the whole clavicle which is practically rudimentary. On both sides the inner half suffers most and is practically absent in the right bone and almost so in the left, while the outer half is still clearly visible. This seems a somewhat unusual form of the condition. Fitzwilliams[1], in an article in the Lancet on cleido-cranial dysostosis, reviewed 60 cases and found the sternal end alone represented, on the left side in 23 and on the right in 27, while the cases where the acromial end alone was present were only 1 and 2 respectively.

Usually this condition is considered to be due to a defective condition of bone developed in membrane, and as such can be contrasted to achondroplasia which is held to be a disease affecting the bones developed in cartilage. Assuming these views to be correct one would feel almost inclined to look upon the two diseases as being diametrically opposed, with exactly opposite manifestations and, perhaps, caused in one case by an excessive activity of a factor in bone formation which is deficient in the other. It is true that in achondroplasia there may be some slight interference with membrane bones as e.g. the hard palate but this seems to be due, as Jansen[2] holds, to actual pressure. We shall refer to this later.

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(1) Fitzwilliams. Bibl.87
(2) Bibl.88. loc.cit.

Recent investigations on the development of the clavicle, however, do not quite confirm our views on the dermal origin of the clavicle. It is now stated by several observers to be developed in cartilage or rather in "precartilaginous tissue". Prof. Fawcett[1] in his article in the Journal of Anatomy and Physiology, states that he finds abundant cartilage cells in the inner side of the clavicle in an embryo of 18-19 m.m. but without seeing any in the outer half, although ossification is quite as advanced here. At a somewhat earlier stage when the embryo is 17 m.m."a few cartilage cells can be distinguished in the inner segment, but none can be made out in the outer segment", but at this stage "ossification has commenced in the pre-cartilaginous tissue". From this description it would seem that cartilage, although it certainly is found in the clavicle, at a later stage, is not actually the tissue in which ossification starts and appears in the inner segment more or less simultaneously with the bone, but in the outer segment its appearance is very definitely preceded by ossification. This cannot be considered the normal formation of bone in cartilage but whether this modified ossification renders the collar bone subject to the same morbid influences which act on the bones of the cranial vault, in which there is no question of cartilage

(1) Prof.Fawcett. The Development & Ossification of the human Clavicle. Bibl.90
(2) Keibel & Mall. Bibl. 88. pg. 579

ever having been present, remains to be investigated.

It is however, clear that the two segments of the clavicle show some difference in their formation, the outer half showing cartilage later. The outer segment, however, is first laid down. Keibel and Mall(1) mention that in an embryo 11 m.m. long, an "ill-defined mass of condensed tissue" was seen to extend from the acromion about a third of the distance to the tip of the first rib.

What bearing these findings have on the origin of the deformity of the clavicle in achondroplasia and whether they may ultimately throw any new light on the origin of this disease cannot be decided till a sufficient number of cases have been carefully investigated. From the early date and the peculiar mode of its ossification, direct from "pre-cartilaginous tissue" and in a slightly different manner in its two component segments; but more still because, in a way, it is the meeting point of two such directly opposite conditions as cleido-cranial dysostosis and achondroplasia, one feels hopeful that any investigator, fortunate enough to collect sufficient material, would reap a rich harvest of information if devoting his attention to the clavicle.

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(1) Keibel & Mall. Bibl.83. p. 379.

THE NATURE OF ACHONDROPLASIA.

When an attempt is made in the light of our present knowledge, to decide which of the many suggestions as to the actual cause of the disease has the best foundation, one is confronted at once with an almost insurmountable difficulty: the very nature of the disease is obscure. Apart from etiological influences we must have a clear idea as to what tissues are affected and at what stage of their development the interference which results in the deformities described, occurs.

It is generally held that the disease, as usually met with, is one of bone chiefly. Yet Porak[1] expresses himself thus - "We are not dealing with local or, more "correctly, special lesions of the osseous system, for "they are accompanied by profound nutritive disturbances "which manifest themselves by an excessive thickening of "the skin". In the previous pages several other lesions outside the skeleton have been mentioned. It is also commonly accepted that only bones developed in cartilage are affected. Although some bones developed in membrane as the hard palate and some of the face-bones sometimes show changes we may take it that, although not confined to them, the cartilage bones are specially selected by the morbid agent. The important problem to be solved is this:- Is achondroplasia a disease of ossification purely and simply and does previously healthy skeletal

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(1) Bibl. 71. pg. 7.

tissue either fail to receive a stimulus to normal bone formation or receive an abnormal one? Or is it an affection of the pre-osseous and even pre-cartilaginous tissues with a primitive structure, already so adversely affected, that the call for further development, normal though it may be, fails to elicit a response? Even the most recent workers differ on this subject.

Prof. Keith(1) in his last article says - "There is "no arrest in the growth of cartilage, there is only an "arrest of the production of bone in cartilage". This is the view most commonly held.

On the other hand, Jansen in his frequently quoted work comes to a totally different conclusion. It is outside the scope of this Thesis to follow him in his very ingenious arguments. They are based on observations which in the main have been confirmed by others and some of which are entirely new. Amongst these the shortening of the hard palate with great diminution of the antero-posterior measurement of the naso-pharynx, especially in the cases showing a generally flattened profile, the progressive interference with the development of the vertebrae from above downwards and the constant dorso-lumbar kyphosis seem the most important. He holds that the deformities must have occurred before cartilage had been fully developed in the mesoblast, in other words, while it was still soft and easily moulded.

(1) Bibl. 94. pg.194. (The underlined words are in italics in the original).

He argues that the combination of deformities met with in achondroplasia can only be explained by assuming a pressure applied chiefly to the cephalic and caudal extremities of the foetus and in an absorbingly interesting chapter[1] shows why, in his opinion, the amnion is at fault. A certain excess of amniotic fluid will cause this enveloping membrane to approximate that shape which can accomodate most and this of course is a globular one. During the first few weeks the consistence of the embryo is little firmer than that of the amnion and during the 3rd week the foetus lies normally curled up. Even a slight accentuation of that curve does not affect the very soft tissue at that time. But when the soft, mesoblastic pre-osseous tissues are just beginning to get stiffened by the appearance of cartilage within them (5th and 6th week of embryonic existence) two new factors are added. Firstly, this is the period of what Jansen calls "physiological stretching" of the embryo, and secondly the developing skeleton has now ~~quite~~ given it a certain firmness which makes it less easily influenced by a tight amnion. If now this latter structure is globular instead of ovoid the embryonic caudal and cephalic pole will bear the brunt of any attempt to stretch the amnion into a shape fitting the straightening embryo. The amnion will have lost its power for evil by direct pressure when the

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(1) Bibl. 88. pg. 56

embryonic supporting tissues have attained a degree of rigidity sufficient to overcome the thin amnion. It is before this stage has been reached that the deformities in the skull and pelvis and the spinal curvature are produced. But as the amnion yields to the firmer embryo the increasingly ovoid shape of the amniotic cavity increases the tension in the fluid it contains and this affects the intra-embryonic circulation and causes a general ischaemia added to the local ischaemia at the actual points of contact at either pole. This general ischaemia occurs just at the time when the limb-buds appear which, lagging much behind the trunk in development, are in a stage when the pre-skeleton is very easily affected.

I believe that Jansen has made out a strong case for his contention that the morbid influence manifests itself very early in foetal life, between the 4th and 7th week. He proves it by showing the undeniable correspondence between the times of the scleroblastema formation of the various parts of the skeleton and the degree of interference with their growth in achondroplasia.

From what has been said about the clavicle, I should feel inclined to fix the date at which the actual morbid process started, in James R's case at least, about the 6th week of embryonic life, basing this opinion chiefly on the difference between the outer and inner end(1).

(1) Prof.A.Thomsom. Osteology. Bibl.60A. pg.180

If this supposition as to the time of onset be correct, there must be something abnormal in the cartilage when it is laid down and the condition cannot be a disease of ossification in the sense that defective ossification occurs in healthy cartilage but it must be a retardation of development in cartilage, which is already potentially morbid. Whether this can be demonstrated histologically is a different question. It seems highly unlikely that in an embryo at thus early a stage of development, even if abnormalities in the developing cartilage were found, one could prove that the subject dealt with was fated to grow into an achondroplast.

The question is intimately bound up with that of normal ossification. Our ideas on this subject are more or less in the melting pot at present, but some light has been shed on it by Prof. McEwen(1) and especially by Prof. A.C.Geddes(2) in an article on the origin of the osteoblast, where he records that by an original method of staining and taking micro-photographs of preparations of developing bone, cells were seen to migrate from the ectoderm, through the periosteum to enter cartilage and act as osteoblasts. This is shown in most beautiful illustrations. The author concludes:-

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(1) Bibl.72 & 76. loc.cit.
(2) Bibl.91 loc.cit. pg. 175.

"There is evidence which makes it probable though by no "means certain that -

1. Bone derives from the ectoderm and not from mesoderm.

2. Osteoblasts arise from the cells of the ectoderm, and migrate as individuals to the sites of bone formation, passing through the periosteum en route.

3. .....

4. Periosteum far from being an osteogenetic membrane, is a limiter of bone formation.

5. Cartilage, a mesodermal tissue, has, when it precedes bone, the function of providing a scaffolding upon which the osteoblasts can move.

6. Osteoclasts are composed of the fused bodies of one or more cartilage cells, with numerous osteoblasts living within the protoplasmic mass as cell inclusions (multipli nuclei)."

If this "probability" be confirmed, and, knowing the quality of Prof. Geddes' work and his scientific restraint in drawing conclusions, one can hardly doubt this, a new light is thrown on the actual cause of achondroplasia. The primary abnormality, as is obvious from Kaufmann's account of the histological appearances in his cases, occurs in unossified cartilage. Row-formation and the other changes preparatory to true bone formation are absent or extremely irregular. Through some morbid influence the bone does not adequately prepare itself to perform its functions as a scaffolding for osteoblasts. Once assuming the migration of cells of ectodermal origin, what attracts

them to the field of their activities? I think that, in the light of what we know about cell-migration, the most likely cause is chemio-taxis. Surely then, it is not too speculative to surmise that the anatomical defects in pre-osseous cartilage are accompanied by a functional defect, that of deficient attraction of osteoblasts. This is a mere hypothesis but then all our theories on the nature of the disease are of that nature. This theory seems to me to have at least the merit that it leaves us free to look for the cause of this defect of the cartilage somewhere outside the tissue mainly affected and to assume a morbid factor which, though it shows a preference for cartilage, may act on other tissues as well. And that achondroplasia is a general disease, and is not limited to bone only, needs no further emphasis at this stage.

ETIOLOGY.

If the nature of the disease has given rise to a variety of opinions, the discussion of the actual cause underlying this deficiency in the cartilage is still more contentious.

Jansen(1) gives a survey of the different opinions on this subject. Parrot(2) speaks of a congenital nutritive disturbance of the cartilage germ cells. This gives a pretty accurate idea of the nature but not of the cause of the condition. De Büch(3) looks upon the achondroplast as the last of a line of degenerates. The now well-recognised stigmata of degeneration are mostly absent. Apart from that, as Jansen remarks, achondroplastic women frequently bear normal children. Some observers speak of a separate race. On ethnographical grounds one can hardly take this view seriously. Achondroplasts have been found all over the world and amongst the most widely different races. Also, as Jansen remraks, as natural labour is practically out of the question, one of the conditions essential to the existence of a separate race is absent.

Heredity is of course a commonly observed factor and we refer the reader to the section on "Dwarfism" in the Treasury of Human Inheritance for reliable information

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(1) Bibl. 88. pg.56
(2) Parrot, Bibl.26. pg.448
(3) De.Büch. Bibl.53
(4) Rischbieth. Bibl.89. pg.335.

and genealogies of well-established cases confirming this. Personally I have seen a case of a girl, Edna W. aged 6, who showed unmistakeable signs of slight achondroplasia with typical hands and the usual facial expression, 34" high, with the mid-point above the umbilicus, straight but stunted limbs and marked lordosis. She has three permanent teeth and the remaining milk teeth are normal. There are 4 more children in the family of which the younger two girls, aet. 18 and 16 respectively, shows signs of slight achondroplasia. The mother is a perfectly healthy woman. The father who is an engine driver could not be induced to show himself but is said to be much below the average in height. He is quite strong and healthy. His wife told me that the three younger children were exactly like him and that they all "had the same sort of hands." His father and all his brothers are said to be very much like him and, as far as his wife knows, for generations these slight deformities have been of constant occurrence in the family to which he belongs. Many similar instances are on record.

The interesting fact has been published by Kanowitz of Vienna(1) that in the Italian town of Bergamo, dwarfs with typical achondroplastic characteristics are very numerous, so much so that it almost appears as if the disease were endemic there. No explanation of this

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(1) Max Kanowitz. Bibl.93.

is given in the British Medical Journal where a note is printed on the original article in La Pediatrie.

Placental changes causing interference with the nutrition of the ovum, pressure of the umbilical stalk on the limb-buds and lack of expansion of the skin have all been advanced as possible causes. The evidence on which these opinions are based is so slender that it seems hardly necessary to discuss them.

Jansen's theory of pressure and pressure alone as the cause of the condition does not seem to me to be proved beyond a doubt. I own that it is a better explanation of the appearances of head and face, spine and pelvis and many of the minor changes than any other. To repeat his argumentsto prove amnion pressure to be the mechanical cause of the deformities, would mean copying a large part of Jansen's work, the careful study of which will not fail to interest the reader. There can be nothing but admiration for the logical way in which he analyses the nature of the malformation and shows it to be extremely unlikely that anything but pressure applied in the way described on page 78, could cause this combination of deformities. So far I am quite prepared to accept his views. There is good reason to believe that the amnion has the power to influence the shape of the foetus. Jansen says in a note(1) - "His(2) attributes

(1) Bibl.88. pg. 59
(2) His. Anatomie menschlicher Embryonen. Bd.II.pg.36.

"the formation of the normal neck-bend in the embryo "(between the 15th and 21st day) to a pressure of the "amnion, i.e. he supposes the embryo to grow more rapidly "about the 3rd week than its amnion sac....."
"We mention this because it suggests the idea that "achondroplasia might be the mere pathological accentua- "tion of a physiological function".(1) I should like to suggest instead of this that many of the deformities in achondroplasia might be the result of a physiological function in a pathological embryo. Surely, if pressure were the sole determining cause and if as the result of this, in the limb at least, defective blood supply were to blame(2), we could not find hypervascularity of the epiphyseal cartilage such a prominent feature. Besides the explanation of several of what he calls "the non-characteristic symptoms" by pressure only is far from convincing. We quite fail to find any connection between the thickened subcutaneous tissue and the increased pressure. The interference with the pituitary gland also seems hardly likely to have as its cause physical compression of the developing organ. This has already been emphasised on page 55 of this treatise.

I have already indicated that a general, non-mechanical influence must act on several different structures and gladly though I accept pressure exercised by the amnion as a most ingenious and probably correct

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(2) compare page 88.
(The underlined words are in italics in the original.

way to explain the nature of the deformities and the multiplicity of their varieties, I cannot without further proof agree that this change in pressure can affect a perfectly normal embryo. Whether we deal with a tissue in which the resistance is so much weakened by disease and especially by the abnormal condition of the cartilage, that even the normal pressure of the physiologically active amnion may cause deformities or whether a somewhat excessive pressure due to very early hydramnion or any other cause is a sine qua non, we have no means to decide. I am, however, of opinion that pressure only produces the deformities characterising chondrudystrophia, where there is a pre-existing disease of the embryo. The cause of that disease is the real problem at present.

Various intoxications have been mentioned amongst which of course syphilis and alcohol take a prominent place. But before we fix on any actual agent we must determine whether the cause is maternal or fœtal. Against the former is the fact that usually an achondroplast has a healthy mother and very frequently healthy brothers and sisters while the pregnancy as a rule runs a normal course. But what renders it almost impossible is a case described by Dr. Hutchinson and quoted by Rischbieth[1] where a healthy woman gave birth to twins, one of which was an achondroplast while the

(1) Bibl.89. Plate P.

other remained quite healthy. We must therefore reject the possibility of the cause being maternal.

Certan[1] and Regnault[2] speak of intra-uterine rickets. Earlier in this Thesis I have given my reasons for considering the two diseases absolutely different.

Porak and Durante[3] believe in an auto-intoxication but whether due to metabolic changes or other factors is not quite clear.

Naturally the eyes of the later investigators have been turned towards internal secretions, either of the ductless glands or tissues elsewhere. Thyroid and thymus have both been suspected but nothing definite has been proved against them. It is true that cretinism and achondroplasia may co-exist but there does not seem to be any causal relationship between the two. In the vast majority of achondroplasts the thyroid is found to be normal[4]. The administration of thyroid extract it may be mentioned although it proves very little, does not have any effect.

But two other internal secretions are not so easily dismissed. The pituitary is always diminished in size and the sexual instincts are always excessively developed, while premature sexual development may be seen.

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(1) Cestan. Bibl.54.
(2) Regnault. Bibl.57
(3) Bibl. 71.
(4) Legry & Regnault. Bibl.63 pg. 547.

(vide page 14). Thus in the case of the former there is an anatomical and in the latter a functional abnormality.

Both the pituitary and the sexual glands have a very marked influence on the growth of the skeleton. That hypertrophy of the former causes giantism is widely known.

Gemelli(1) removed the pituitary in young cats and after some days, during which disturbance of health and metabolism took place, a gradual return to the normal occurred but growth was arrested.

The sexual glands bear a very intimate relation to growth of the skeleton and also to the hypophysis. The pituitary enlarges in castrated animals. With this increase in the size of the gland growth of the subject is hastened.(2) Maisonnave(3) by injecting extract of testicle into animals caused stunting of growth and what he called "stérilisation relative" of the diaphyso-epiphyseal cartilages(4).

In gigantism, in which the pituitary hyperactivity is now universally established as the cause, sexual activity is diminished while in achondroplasia we find the reverse.

Definite proof that the sexual glands or the pituit-

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(1) Gemelli. Bibl.77
(2) Fichera. Sur l'hypertrophie de la glande pituitaire consecutive a la castration.
(3) Maissonave. Contribution a l'etude de l'opotherapie orchitique.
(4) Bibl.88. pg.96.

-ary or both are the cause of the interference with nutrition, which under the influence of amnion pressure produces the achondroplast,, we have not. But although the evidence is purely circumstantial, it all leads to the same conclusions and we believe that when the ultimate cause is definitely established, the above theory will be confirmed.

TREATMENT.

There remains the melancholy task of confessing our impotence at present to deal with the condition therapeutically. Medical treatment after birth holds out little hope of success. Jansen suggests the cautious administration of pituitary extract. It certainly is worth a trial.

Orthopaedic surgery may in some cases correct some of the deformities but even this promises very little relief to the unfortunate sufferer.

CONCLUSIONS.

1. Two definite varieties of chondrodystrophia foetalis can be recognised clinically as well as microscopically.

2. It is a general disease, affecting many tissues but mainly those parts of the skeleton developed in cartilage.

3. A definite diagnosis can always be made with the aid of X-rays.

4. The disease is present before ossification commences in any given bone and results in defective preparation for ossification in cartilage, causing a deficient attraction of true bone-forming cells.

5. It is highly probable that softness of the skeleton due to disease affecting the cartilage, enables mechanical influences, most likely pressure of the amnion, to cause the deformities of achondroplasia.

6. The knowledge we possess of the metabolic influence of the pituitary and sexual glands points to an abnormal function of either or both of these structures as the most likely agent to cause the disturbance in the cartilage and elsewhere.

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