Rowe AW & Mortimer H.
Endocrine Studies: XLII.
A note on acromegaly with the report of a case.
Endocrinology 1934; 18:20-32.

ENDOCRINE STUDIES: XLII. A NOTE ON ACROMEGALY WITH THE REPORT OF A CASE

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The striking picture of aberrant growth characteristic of acromegaly, since the days of Pierre Marie has commonly been ascribed to an overproduction of the internal secretions of the pituitary gland. Further, it has usually been regarded as a late manifestation of disturbed glandular function, appearing after closure of the epiphyses has inhibited further longitudinal growth of the long bones. Thus a simple grouping has been to recognize gigantism without acromegaly as the result of hyperfunction during the prepuberal and adolescent years, acromegaly without gigantism as the expression of an overactivity, the onset of which falls in the period of maturity and after epiphyseal closure, while the combination of the two has been interpreted as evidence of a long-continued period of hormonal overproduction beginning in childhood and continuing unchecked into the time of an established maturity. Ultimately, the gland tends to undergo functional involution to an ultimate state of hormonal failure, leaving, however, the striking changes in skeletal development as immutable residua of the earlier status. Tumor growth, at least in proportions recognizable by roentgenographic examination, is a far from inevitable background for these conditions, although in those cases in which surgical intervention has been practiced, tumorous growths are usually reported. Biopsy being impracticable in this situation it is to be regretted that postmortem histological examinations are not more frequently obtainable.

Recently the radiographic and anatomical study of a series of skulls from known cases of pituitary disease (1) by one of us (H. M.) has indicated the need for some revision in the simple classification given above. While the majority of the hyperpituitary cases will follow broadly the general grouping as initially stated, the appearance of varying degrees of acromegalic cranial changes in individuals entering the second decade of life and with demonstrably open epiphyses, calls for a recognition of an earlier onset of the characteristic skull changes in at least a portion of those individuals who at some time in youth have a transitory period of pituitary hyperfunction. The term "sub-acromegaly" ("forme fruste") might properly be applied to this single category and the study of such individuals later in life, when the gland has normalized or passed to a typical hypofunctional level, offers, with the latter group, at least, the interesting possibility of a reconstruction of the glandular history of the individual. Our added knowledge of today serves but to add emphasis to the fact, long recognized, that the chronology of the glandular malfunction,

in terms of the growth and developmental possibilities of the individual, plays a primary rôle in determining many of the more salient changes which characterize the varied end results of the putatively common cause.

With this brief preliminary statement, a short report may be made of a partial study recently carried out on a typical case of acromegaly. The patient in question, J. E., is a young man of 26, well-known in professional

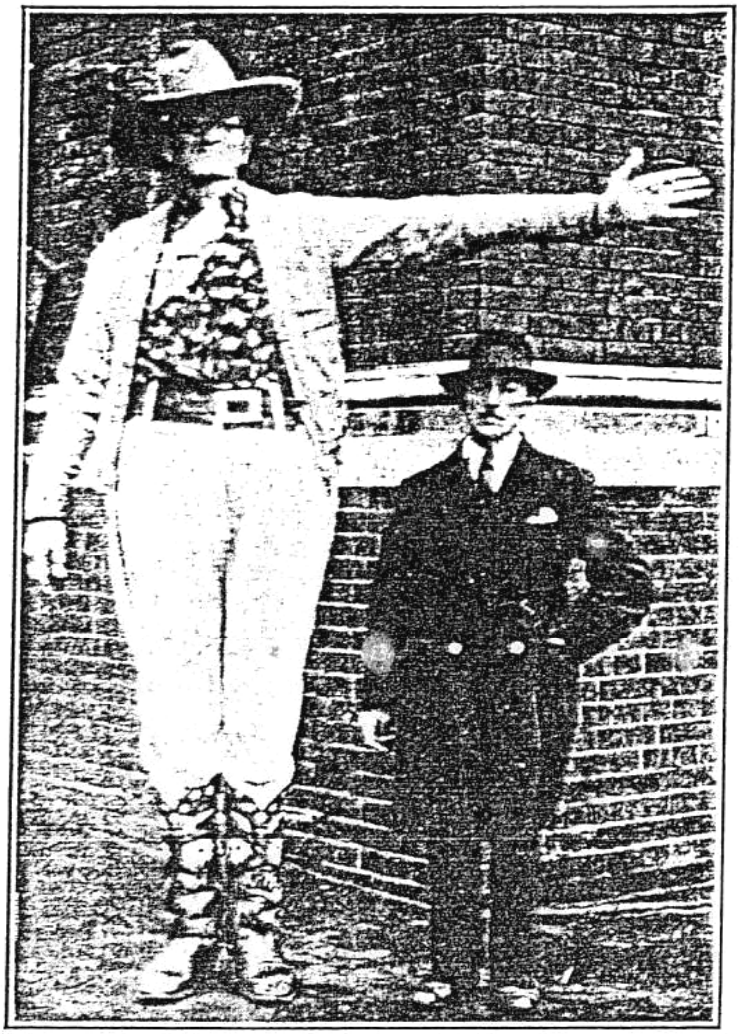

Figure 1. The patient with a man of average size.

circles, where he has appeared as a giant for a number of years. While fulfilling an engagement in Boston, he was kind enough to give us an opportunity for study at such times as his professional activities permitted.*

No formal history was secured from the patient, partly through lack of time and further as it is anticipated that he will be thoroughly studied at a later date. He reported the fact, however, that his principal period of rapid growth began in his eighth and terminated in his sixteenth year. Minor ailments of childhood were reported but none of apparent significant association. He was athletic during his school days and participated in various competitive sports. Football was forbidden on the grounds of possible injury, a most wise interdiction as the radiographic examination of the long bones makes clear.

*It is with great pleasure that we acknowledge our indebtedness for the cooperation, at no little personal inconvenience, which made these records possible.

A thorough physical examination was likewise postponed to a later date. The present study was largely confined to the purely objective data as conforming best to the patient's freedom of time and his convenience. The results may be briefly recorded under the several suitable captions:

Physical Measurements. The more significant of these may be presented in tabular form.

TABLE I
PHYSICAL MEASUREMENTS

Standing Height	228.6	cm.
Span	236.2	cm.
Sitting Height	110.5	cm.
Sitting Height, Index	0.483	cm.
Head, Circumference	60.5	cm.
Neck, Circumference	43.5	cm.
Chest, Circumference (exp.)	119.0	cm.
Chest, Circumference (insp.)	129.5	cm.
Waist, Circumference	107.0	cm.
Hips, Circumference	130.0	cm.
Weight	163.3	kg.

The sitting height index is low, a usual finding in all cases in which the great height is due to undue longitudinal overgrowth of the long bones. By the Dreyer standard of so-called trunk height, the patient is 33 per cent above his predicted weight. Dreyer's subjects, however, were individuals of relatively normal bodily configuration, and the short trunk length influences the prediction unduly. Calculating the appropriate trunk length by multiplying the standing height by 0.525, the normal average index, his predicted and observed weight fall within 3 per cent of each other, a record far more in accord with the facts.

The hands were 25.4 cm. long, the feet 33.0 cm. Numerous other measurements showed relatively normal mutual relationships.

Urine. The output for 24 hours was 3720 cc. with a specific gravity of 1.009. A minimal trace of albumin was recorded and the indican content was notably high. Examination of the sediment showed from 4 to 8 leucocytes and from 2 to 4 hyaline casts per high power field. An occasional blood disc and rare finely granular cast were likewise reported. The urine gave evidence of some degree of renal irritation, the suggestion receiving confirmation from the blood chemistry, as will be shown later. The nitrogen partition examination gave the following results:

TABLE II
URINARY NITROGEN PARTITION

Substance	Gms.	Per Cent
Total Nitrogen	14.37	....
Urea Nitrogen	11.22	78.1
Uric Acid Nitrogen	.29	2.0
Ammonia Nitrogen	.56	3.9
Creatinin Nitrogen	.74	5.1
Residual Nitrogen	1.56	10.9

The protein exchange is certainly not high for a man weighing 163 kilograms but still is probably at a maintenance level. The high residual nitrogen correlates with the evidence of renal impairment. Urea, naturally, is slightly low, the other values relatively normal.

Blood Morphology. The haemoglobin was 88 per cent (Dare) and the red count, 4,980,000, determining a color index of 0.88. The leucocyte count was 9500, while the differential count is given in the next table.

TABLE III
DIFFERENTIAL LEUCOCYTE COUNT

Neutrophiles		43.0
Lymphocytes—		
Small	39.5	
Large	2.0	41.5
Endothelials—		
Trans	7.0	
Mono	0.5	7.5
Eosinophils		7.5
Basophils		0.5

The slight lymphocytosis is a usual finding in the various endocrinopathies and the eosinophilia is characteristic of the various types of pituitary disorders. The coagulation time (Brodie) was the low normal value of 2.5 minutes.

Blood Chemistry. The somewhat thorough study of the blood was made by Dr. Richard Wagner, to whom the authors express their appreciative thanks.

TABLE IV
BLOOD CHEMISTRY

Constituent	Amount
Cells	38.7 %
Plasma	61.3 %
Total Nitrogen (plasma)	1.34%
Albumin	4.58%
Globulin	3.33%
A:G Ratio	1.38
Fibrinogen	0.44%
Non-Protein Nitrogen	40 mgm.
Urea Nitrogen	19 mgm.
Uric Acid	7.5 mgm.
Sugar	117 mgm.
Sodium Chloride (plasma)	646 mgm.
Inorganic Phosphorous	3.6 mgm.
Calcium (serum)	10.2 mgm.

But few comments are necessary. The serum albumin has a low normal value while the globulin is definitely high. This lowers the ratio significantly and offers another evidence of potential renal impairment. This conclusion of lowered renal permeability is further supported by the somewhat high values for the non-protein and urea nitrogen and the plasma chlorides. The high blood uric acid, both absolutely and relatively greatly

increased above the slight increments of the foregoing constituents, is referable to the pituitary condition and characteristic of it among the endocrinopathies. The blood sugar is a high normal, an observation referable either to the nervous instability of the patient or evidencing a tendency toward a hyperglycaemia that may be remarked in pituitary hyperfunction. In the present instance we incline to the first explanation as objective evidences are lacking to define a present hyperactive condition of the gland.

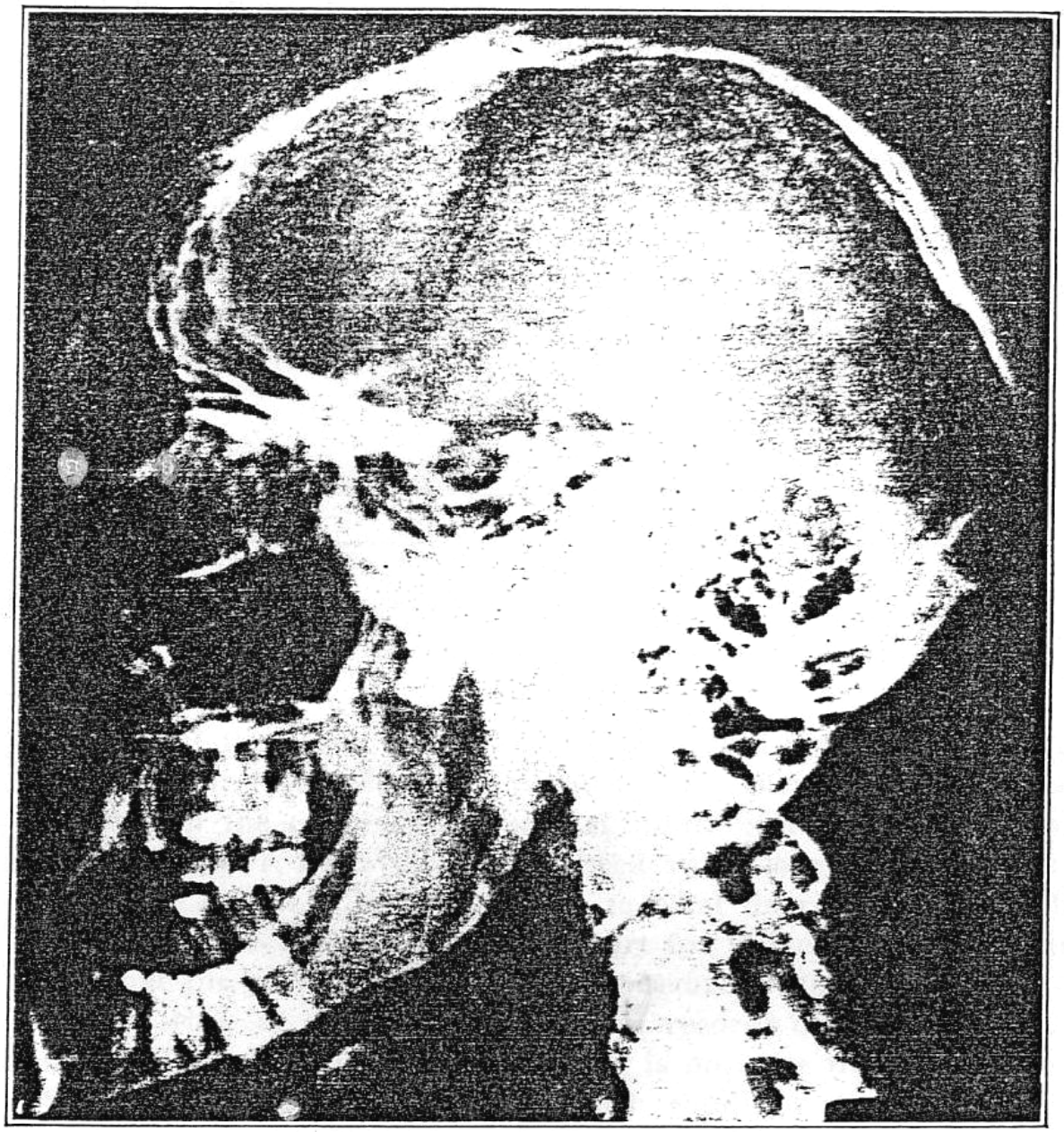

Figure 2. Lateral skiagram of skull.

On the contrary, it is apparently in a state of downward functional transition. The other constituents fall within the conventional limits of the normal.

Respiratory Metabolism. Some little difficulty was experienced at first in securing this datum as the large volume of the respiratory exchange precluded the use of any of the usual closed circuit types of apparatus

which constitute our usual practice. By adopting the open circuit approach and using Tissot spirometers of 125 liter capacity, a series of reasonably satisfactory measurements were secured. During the preliminaries the patient told us that a basal rate measurement had been attempted upon him some years previously. It was abortive as obviously a closed circuit apparatus was used and he exhausted the spirometer in a brief space of time with results which had apparently disturbed him. This recollection, together with his own nervous instability, undoubtedly influenced adversely the results of our own measurements. His first observed rate was 3245 calories with an R.Q. of 0.97; the second attempt yielded a value of 3107 with the more plausible coefficient of 0.89, and the third and last measurement gave a value of 2969 cal. based upon the R.Q. of 0.89 again observed or 2916 cal. if the conventional practice of assuming an R.Q. of 0.82 be followed. In our opinion, these results give undoubted evidence of the influence of an emotional factor which precluded the measurement of the true basal level in this case as it has in so many others encountered during the past decade. Assuming the lowest value 2969 as the most nearly representative value, comparison with the usual standards of prediction give the following results:

TABLE V

Prediction	Amount	Deviation
Harris-Benedict	3279	−9%
Aub-du Bois	3048	−3%
Same, Boothby modification	3110	−5%
Dreyer	3051	−3%

Use of the lower value of 2916 cal. would depress these deviations no more than an inconsiderable 2 per cent. In other words, all of these values fall within the conventional normal limits of deviation from prediction. As noted above, however, the observed value is a maximum and the true basal rate certainly lower although to what degree it is impossible to say and idle to speculate. Further support for this contention is found in the fact that the pulse rate during the measurements was from 78 to 80 per minute, while at other times consistent records of from 58 to 60 were secured. The upward trend in the rate is no more than one other evidence of nervousness during the test, which condition the patient also subsequently affirmed. The respiration rate was 10, the temperature 98.6° and the blood pressure 146 mm. systolic and 90 mm. diastolic.

Carbohydrate Metabolism.- It was impossible in the limited time available to secure a complete set of galactose tolerance tests. Only one morning could be given to this and a 20-gram dose was selected as a positive response would show a depressed, a negative test normal or increased tolerance. The results follow:

TABLE VI

GALACTOSE TEST. 20 GMS.

Time of Urine Collection	Sugar	Nitrogen Elimination
5 A.M. to 7 A.M.	0	2.95 gms.
7 A.M. Test Meal administered.		
7 A.M. to 9 A.M.	0	2.71 gms.
9 A.M. to 11 A.M.	0	1.40 gms.

The usual precautions were observed, the test was negative, and the sugar exhibited a protein sparing action so far as the urine nitrogen is to be regarded as defining.

The galactose tolerance was not depressed; the single test fails to indicate if it was normal or increased.

Figure 3. Skiagram of frontal bone above the sinuses.

Eye Examination. The routine examination was carried out by Dr. H. M. Emmons, to whom we express our indebtedness. Vision with glasses was recorded as: right, 10/30; left, 10/10. The pupils were 4 mm. in diameter and were equal and round. Light and consensual reactions were reported as slightly sluggish; accommodation, normal. Of the right fundus it was reported: "The arteries appear normal in size and shape; veins slightly dilated; optic nerve appears slightly pale; disc margin hazy." On the left, "the veins are more dilated than on the right, the nerve head shows a slight papillitis; the optic nerve is slightly pale."

Both fundi show yellowish tinge, the left more pronounced than the right."

The form fields showed a marked upper cutting, recoverable on raising the lids. The color fields and the blind spots were normal.

Roentgenological Examination. The lateral skiagram of the skull shows characteristic "Type 1" acromegalic changes (1); in all the com-

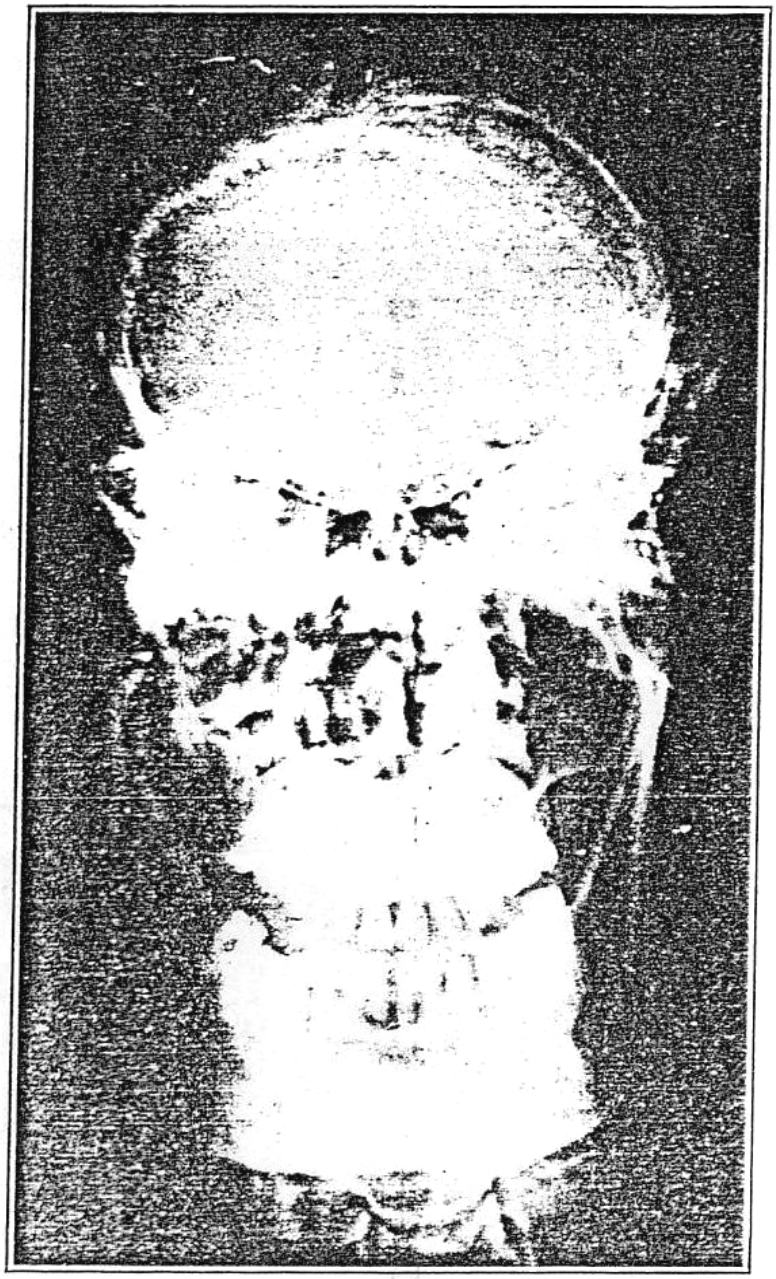

Figure 4. Antero-posterior skiagram of skull.

ponent bones of the head there is evidence of overdevelopment of cancellous bone, as well as overgrowth of those structures normally developed in cancellous bone.

The most striking changes are seen in the frontal bone. The frontal sinuses are huge (Figs. 2 and 3); in fact, they are the largest we have seen either clinically, in roentgenograms, or in the museum material collected

in America and England. Laterally, the sinuses extend to the zygomatic processes of the bone (Fig. 4); vertically, they are extensive, the left sinus measuring 68 mm. in height and reaching about half way to the coronal suture; antero-posteriorly, they are 65 mm. in depth and extend more than half way back in the orbital plate of the frontal bone.

The sphenoid, ethmoid, and maxillary air sinuses (Fig. 2) are very large and the mastoid cells (Fig. 6) are the largest and most extensive we

Figure 5. "Close-up-view" of antero-posterior skiagram of frontal bone, showing sinuses and their extensions.

have seen; there is a continuous mass of pneumatization between them and the frontal sinuses (Fig. 2).

In the calvarium the most marked change is seen in the frontal bone above the sinuses (Fig. 3), and here is revealed the fundamental nature of the bony changes which are responsible for the various deformities, found in this condition. Here the bone measures 13 mm. in thickness, and of this some 9 mm., or five-sixths, is seen to be diploë. The outer table of the bone is clearly defined, but not thickened. The coronal suture is already

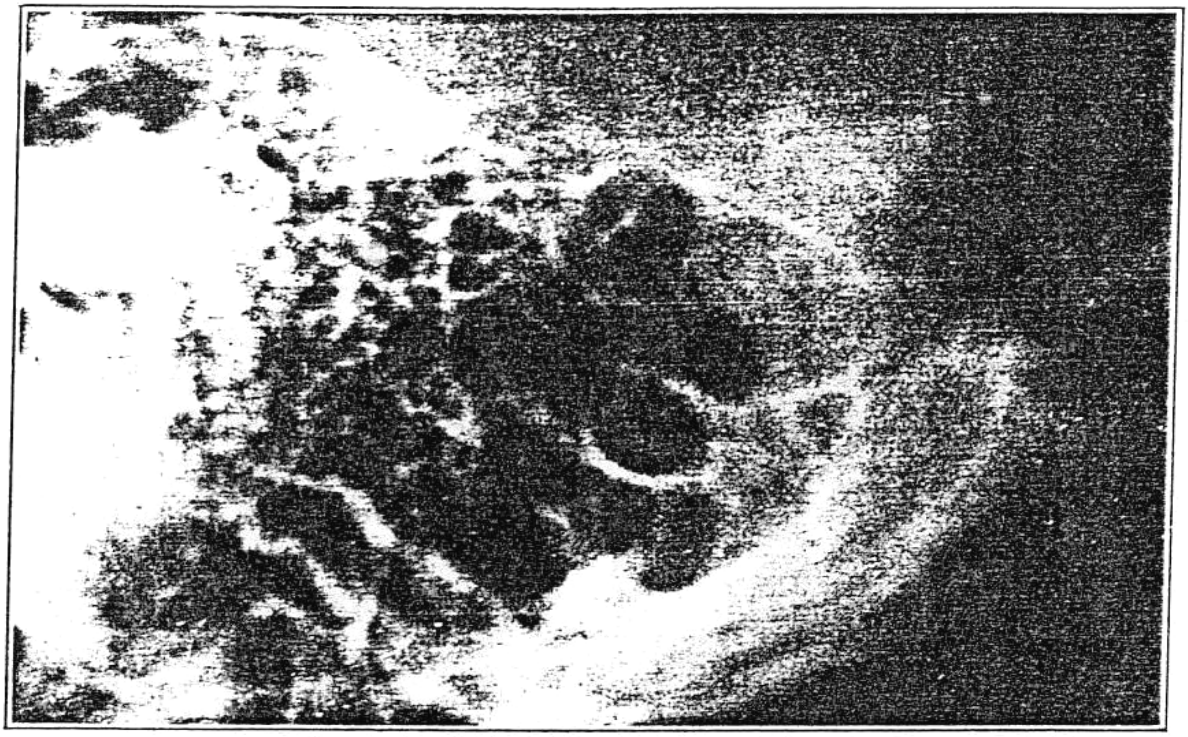

Figure 6. The mastoid air cells.

ossified—the patient is 26. The inner table is not markedly thickened, but there is evidence at certain points of some sclerosis extending into the adjacent diploë.

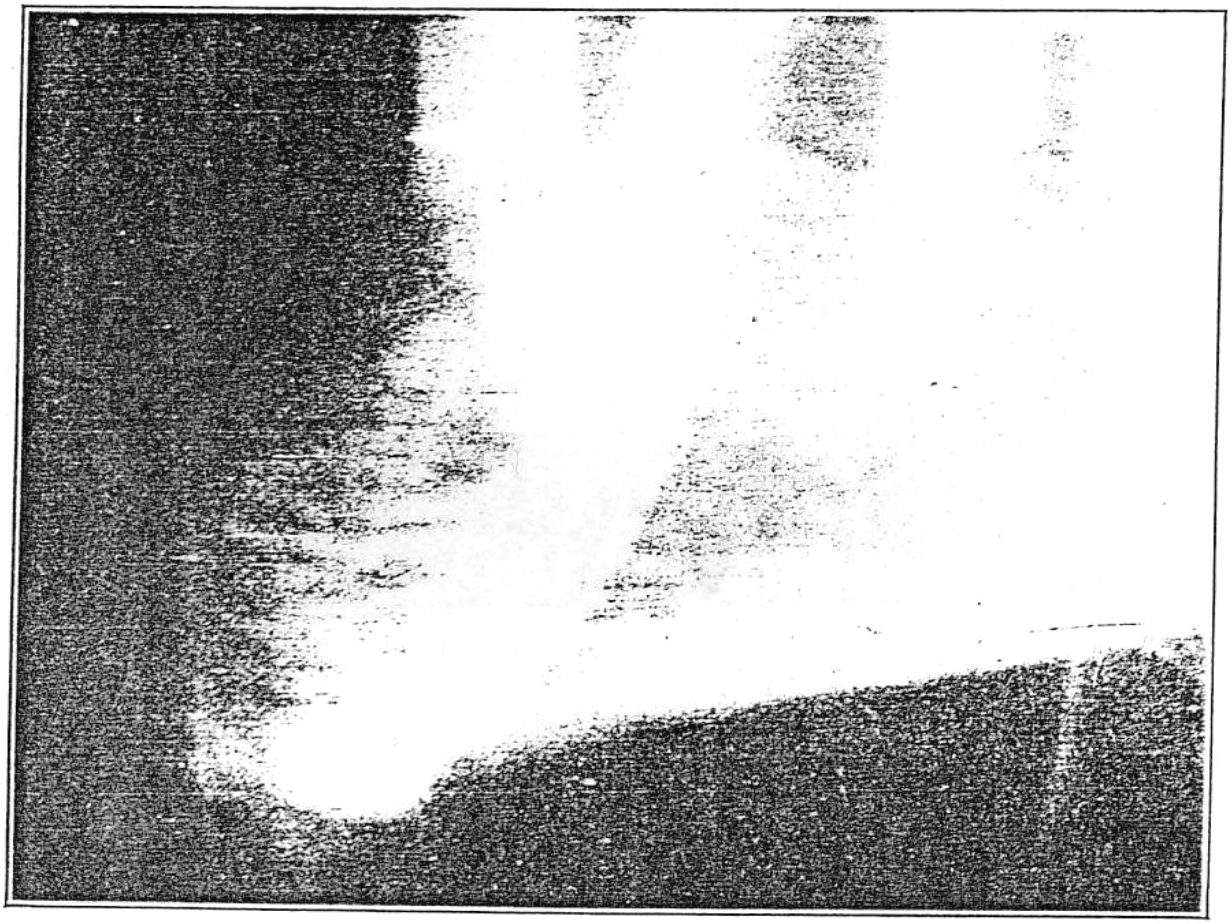

Figure 7. The symphysis menti.

"The sella turcica (Fig. 2) measures 11 mm. x 14 mm., and the floor is somewhat depressed and irregular, suggestive of intrasellar tumour."

Although prognathism, in the true sense, is not markedly present, there is considerable progenium, and a close-up-view of the symphysis menti (Fig. 7) shows clearly how this result has been produced. The symphysis is seen to be composed of rows of horizontally-placed, thin-walled, expanded cancellous bone spaces—progenium resulting mechanically from the expansion of the constituent elements of the bone, and not in any real sense from deposition or growth of new bone. Indeed, the mandible is obviously

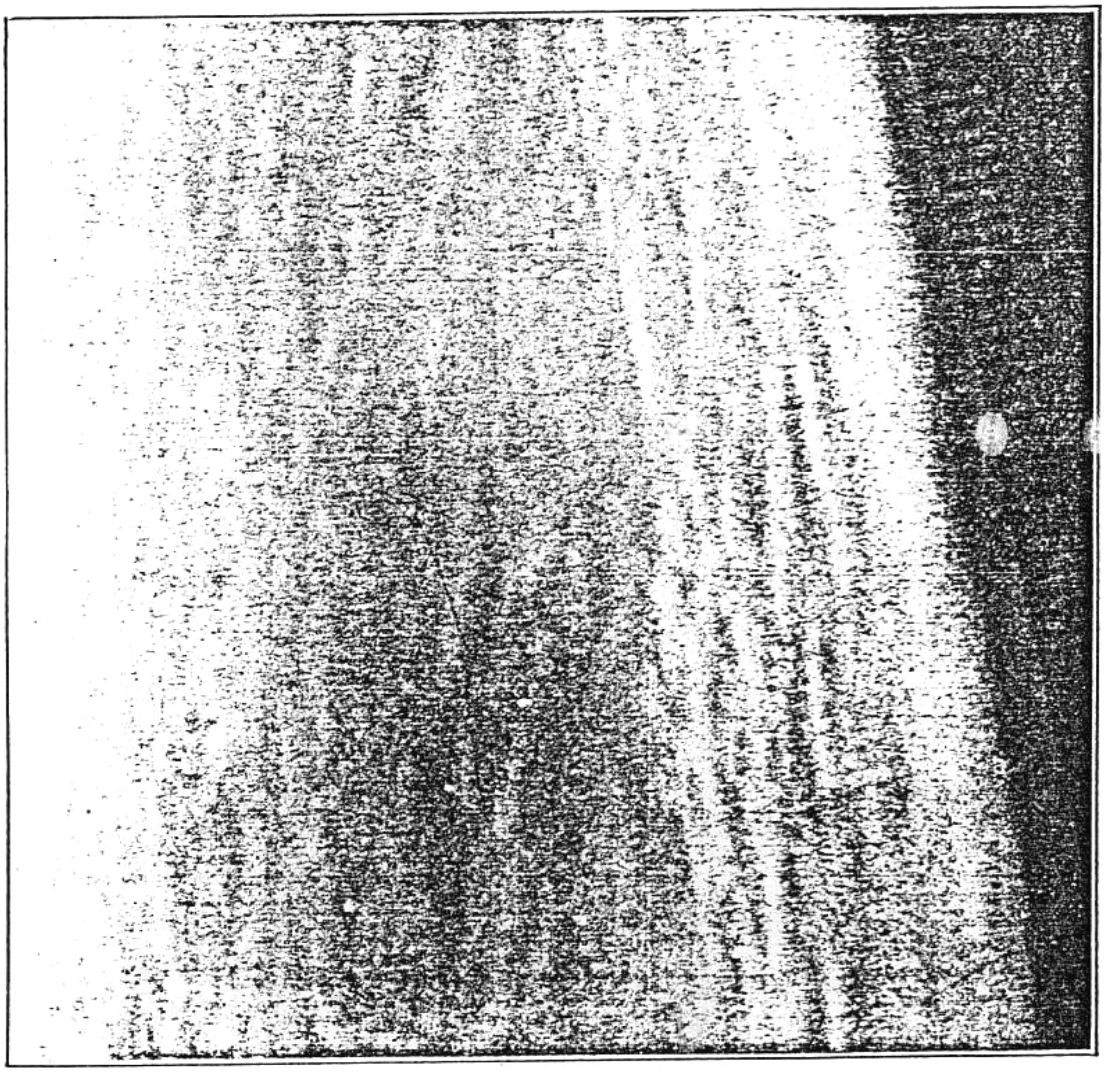

Figure 8. Skiagram of middle third right femur.

rarefied. Although, as already noted, there is hyperpneumatization of the maxillary antra, which has a definite influence on the size of the superior maxilla; the degree to which an antrum may expand is limited by the fact that it is but a single air-cell, whereas, if the cancellous spaces in the mandibular rami expand also to the maximal degree, the total increment in length, so gained, may easily surpass any gain, in a forward direction, of the superior maxilla; thus progenium will result.

The antero-posterior cranial skiagram (Fig. 4) shows clearly the extreme degree of pneumatization of the face. On both sides, above the

upper limits of the frontal sinuses, can be seen areas where overexpansion of trabeculae has caused their breakdown, and the formation of additional sinus-area, the limits of which (Fig. 5) are indicated by the strengthening calcification of remaining, supporting trabeculae. Such areas show the mechanism whereby the anatomical sinuses have reached their present high "growth" in the bone—especially on the left side. This photograph, also, shows the extent to which the frontal sinuses extend laterally into the orbital plates, a fact which, to us, is indicative of early vigorous growth of the sinus.

Figure 9. Skiagram metacarpo-phalangeal joint of thumb.

Skiagrams of the phalanges (Fig. 9) show great longitudinal expansion of cancellous bone. There is no "anchor tufting," nor is there anywhere, in the osseous system of this patient, evidence of either osteo-arthritic or cystic change.

The femoral skiagram is of much interest because of the great length of the bone. From the tip of the great trochanter to the lower end of the internal condyle, the bone measures 80.6 cms. Three 14 x 17 in. films were required to skiagraph this bone with its joints. Figure 8 is a "close-up-view" of the roentgenogram of its middle third, with a celluloid millimeter

scale laid on the film. About three-quarters of the diameter of the bone is shown, as can be seen from the position of the medullary cavity. Noteworthy is the relatively poor proportion of cortical to medullary bone, and the great length of the thin-walled cancellous spaces. One of these, about the middle of the picture, can be seen to measure 22 mm. in length.

From the foregoing it will be seen that in this patient there is one basic change in all the skiagrams—overexpansion of cancellous bone. This accounts for the thickening of the skull, the enlargement of all the paranasal and other sinuses, the jaw deformity, the huge hands and feet, and finally it is this mechanism by which the patient has attained his great height.

SUMMARY

Recent radiographic and anatomical studies in established pituitary cases have demonstrated that acromegalic changes, primarily in the skull, are not confined to adult years. Further, aborted or subacromegalic types have been demonstrated by radiography in children presenting characteristic evidences of pituitary dysfunction. Finally, tumor growth, at least of a magnitude demonstrable by x-ray, is by no means an essential feature of the condition.

In illustration, the paper presents the results of a partial study of a well-known acromegalic giant. Fairly complete physical measurements are supplemented by blood and urine studies, the respiratory and carbohydrate metabolisms and an eye examination. Certain features, as the low sitting height index (0.483), bulky urine (3720 cc.), eosinophilia (7.5 per cent), high blood uric acid (7.5 mgm.), are characteristic diagnostic signs. Typical evidences of renal irritation were presented by the urine (casts, blood discs), the blood chemistry (non-protein and urea nitrogen and chlorides), and a low albumin: globulin ratio (1.38) in the blood. His oxygen consumption was recorded as 9 per cent below the Harris-Benedict prediction and was undoubtedly lower as he was not in a completely basal state. The report ends with a number of the plates obtained during the fairly complete radiographic study. The skull findings were typical of the authors' Type 1, showing hyperostosis of the vault with marked expansion of the diploë and extreme hyperpneumatization of the sinuses; there was well defined asymmetrical prognathism.

The sella was 11 x 14 mm., the floor somewhat depressed and irregular suggestive of possible intrasellar tumor. Other plates give additional skull details and show the hands, femur, etc. Overexpansion of cancellous bone is demonstrated in all areas showing marked overgrowth and is regarded as being the underlying mechanism.

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