ACROMEGALY,

WITH SPECIAL REFERENCE TO

ITS ETIOLOGY:

by

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ACROMEGALY,

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The case of Acromegaly which first directed the writer's special attention to the subject came under his notice in 1902. The literature at that time showed an ever-increasing interest in this and allied conditions, the consideration of which by many authors has provided much food for thought. Since that time much research work has been added to that previously recorded concerning internal secretions, their inter-relationship, their inter-dependence, and their compensatory powers. The conception of the disease afforded by the original description by Marie has not materially altered, though the clinical picture has been amplified and detailed, and variations noted, and the etiology more clearly defined. Some notable advances have been made in the physiology and pathology of the pituitary body, and the surgical aspect of the remedial side has attracted much attention of late years.

The oldest medical account of the disease is that of the "Sieur Mirbeck" case by Saucerotte and Noël (1772 to 1779).

In 1839, Magendie described what was probably a case, as hypertrophy of "possibly nervous origin."

The first complete post-mortem was that by Verga in 1869, which revealed a large tumour on the Sella Turcica.

There is a portrait, life-size, of a giant in the Schloss Ambras near Innsbruck, of the date 1553, which reveals acromegalian characters.

There is a skull in the Museum of the Royal College of Surgeons of England which was once possessed by a London phrenologist. This came into the possession of Barnard Davis, and in 1863 he demonstrated that this skull had a similar formation to that of the Neanderthal cranium, the characters and primitive nature of which Huxley demonstrated at that time. Thus the detection of the resemblance between acromegalian and paleolithic crania was made nearly thirty years before the condition of acromegaly was recognised as a clinical entity.

Freund in 1872 definitely mentioned the anthropoid character of the acromegalic cranium. Later, in 1878, Cunningham was struck by this. His description of a case of acromegaly was the first full one in this country, and he was also the first to recognise the relationship between acromegaly and gigantism (Keith). The first account we have of the disease, under the name which Marie applied to it in his original essay, is in his thesis republished in the "Révue de Médecine"[1] in 1886, and the translation of that essay and of the subsequent monographs by

Souza-Leite(in 1890) and by Sternberg (1899) at the instance of the New Sydenham Society have brought the subject widely under the notice of English readers. Thirty-eight cases were recorded by Marie and Souza-Leite up to the latter's publication,and some additional cases collected by the editor of the New Sydenham Society in 1891. Marie's description was based upon two cases personally observed,and five cases,published by different authors,which he claimed as examples of the disease. Up to April 1902,262 cases were on record,with 77 autopsies,in only 4 of which the pituitary gland was not involved (Woods_Hutchinson). Marie described "a group of associated symptoms,the most conspicuous of which was overgrowth of the hands and of the head and face". As a frequent accompaniment, if not as a cause,Marie observed the occurrence of great "hypertrophy of the pituitary body." When Marie first showed his two patients,he expressed the opinion,not without some reserve,that they were abnormal cases of Paget's disease,but in his Essay recognised and examined the differences,and in his Conclusions maintained that Acromegaly(the name he applied) was quite distinct from Myxoedema,Leontiasis Ossea (Virchow) and Osteitis Deformans (as described by Paget in 1876). One of Marie's cases had been admitted to the Salpêtrière as early as 1869. Souza-Leite in 1890 remarked that the disease had,so to speak,no

history, except that summed up in his title, "Marie's Malady." In the period intervening between Marie's first essay and Souza-Leite's work, a number of memoirs and contributions appeared. Souza-Leite remarked that the cause of acromegaly "was not yet known." It is worthy of note that Hadden and Ballance, in 1885, showed a case to the London Clinical Society, which, however, they described as "hypertrophy of the subcutaneous tissues of the face, hands and feet." After Marie's memoir appeared and the disease was named, certain conditions were put in this category which were distinct maladies. One condition to which Marie paid special attention during that period was hypertrophic, pulmonary osteoarthropathy, and he lectured at the Salpêtrière on a case which he had studied in Gourand's practice (Bulletin Médical, December, 1889).

A curious point about the history of this disease is that in 1868 Friedreich published the cases of the two brothers Hagner. These were cases V and VI of Marie's original series of cases of acromegaly, which Erb also considered them to be, while some regarded them as Paget's disease.

Sternberg was able to refer to over 200 cases of acromegaly before the publication of his monograph. In 1894, he specially considered the relations with gigantism, and concluded that the giants' skeletons with abnormal skulls described by Langer were acromegalian. Sternberg also drew attention

to the occurrence of pain and paraesthesiae of the extremities, which had not previously been emphasized, and discussed the probable explanation of the hyperplasia of the thymus.

Marie in 1896 described the alteration in the hand as occurring in two types, "en large" and "en long". The application of Röntgen rays was signally successful in demonstrating clinically the bony changes, an advantage which was not possessed in the investigation of the earliest cases.

An important occasion in the history of the elucidation of the nature of acromegaly was the presentation of a paper by Hastings Gilford, some fourteen years ago, before the Royal Medical and Chirurgical Society, on two cases of "premature old age, engrafted upon or running side by side with a condition of immaturity or infantilism." The study of ateleiosis (spontaneous, persistent immaturity) in contrast with acromegaly, and the consideration of the symptom-complex described by Fröhlich as dystrophia adiposo-genitalis, have done much to throw light on the significance of the manifestations of pituitary disease, though the pathogenesis of the pituitary changes is not yet clearly established. It may be said here that the most marked tendency is to regard the specific symptoms of acromegaly as due to an alteration in the function of the anterior glandular lobe of the hypophysis, the alteration being of the nature of an increased activity. The whole

clinical picture of the disease points to its being "the type of a polyglandular disease."(Münzer)(2)

Recapitulation of the Main Symptoms and Signs.

In a well-developed case, the general appearance of a patient is very characteristic. Largeness of extremities, as denoted by the name, strikes the observer. This may or may not be accompanied by general increase in size, but increase in stature is not the usual condition. The expression is dull, the complexion lacking lustre, and there is marked alteration of the features. The face is lengthened and elliptical, the lower jaw being greatly enlarged, prognathism being often present. The nose and lips are hypertrophied, the lower lip being often specially so, and turned down. The tongue is much increased in size, and may constantly protrude. The ears may share in the increase; the orbital margins and the malar bones unduly project, and the temporal regions appear sunken. Protrusion of the eyeballs is common, and muscular defects thereof may be observed. The skull is generally enlarged; distinct bosses thereon do not typically occur, though in many cases thickening along the sutures has been observed. The natural creases and folds of the skin are emphasized, and the nasal and auricular cartilages increasedly resistant. A moderate degree of cyanosis is often noted. The hands and feet are enlarged as a whole, all portions of them partaking, and the

changes being symmetrical. An important point is the disproportion which the extremities present to the size of the limbs to which they are attached. The head is sunken forwards between the shoulders, with the enlarged chin resting on or near the chest. Cervico-dorsal curvature of the spine is a factor in producing this appearance, which, with projection of the sternum, has given rise to the description as "Punchinello." The bones of the trunk are massive, this being readily noticed in connection with the iliac bones, the ribs, and the clavicles. A goître is often present, though this may be obscured by the thickening of, and by the attitude of, the neck. The patient's voice is altered, roughened and deepened: the bearing listless. The skin can be readily folded, but myxoedematous symptoms have occurred in the course of some cases. Thickening of the skin is usually most apparent over the extremities. Radiographs demonstrate that the bones of the extremities are enlarged, but the superimposed soft parts usually share more in the hypertrophy, and here, as in the face, the natural folds are exaggerated. The soft pads are sometimes much increased. In the later stages, muscular wasting, if pronounced, accentuates the alteration in the bones. Pigmentation of the skin may be increased, and excessive perspiration is a common symptom. Circulatory difficulties occur, the heart is often enlarged, and vaso-motor phenomena are

frequently observed,especially in the earlier stages. Dizziness,palpitation,tingling sensations in the extremities,occasional swelling of them,"dead" fingers,and the like occur. Varicose veins on the hands and legs and haemorrhoids have been frequently found. The main blood-vessels of the enlarged parts appear to undergo a corresponding increase in size. Arterio-sclerosis has been often recorded.

The enlargement of the bones of the chest and the tilting forwards of the lower end of the sternum have been mentioned. Sternal dulness in the upper part has been noted. A tendency to bronchitis is often present,as might be expected with faulty circulation and rigid thorax. The thymus gland has been found enlarged,though the connection of this with the sternal dulness has been disproved. The larynx is affected in many cases;its enlargement may be seen and felt externally,if no goitre happen to obscure it.

The teeth have been recorded as enlarged in only one,an early case. They are frequently lost early,but if present,in a typical case,project forwards,from both the upper and the lower jaw,the lower teeth in front of the upper in a considerable proportion. Abnormal increase of appetite and thirst have been observed in several cases. A condition of splanchnomegaly has been recorded. W.W.Graves has called attention to the separation of the teeth,with widening of the alveolar processes,as an important early sign.(Osler) The

lingual hypertrophy may occasion difficulty in mastication and speech.

Glycosuria is a common symptom, and it may be amenable to dietetic treatment and temporary, or, a lasting condition of diabetes may be established and death result from diabetic coma. Pressor substances have been found in the urine in a case where they were found in the tissues post mortem. (3)

The general nutrition of the patient may or may not appear impaired: weakness is a frequent complaint. Increase of strength in the early history has been recorded — this in connection with some of the first cases. Usually the general condition of the patient, before the later stages, is in contrast with the muscular weakness and the readiness to fatigue.

A cardinal symptom is interference with the reproductive organs. Impotence in the male and amenorrhea in the female have been the rule. In cases supervening during physiological amenorrhea, the menses have not been re-established. It was customary some years ago to regard the amenorrhea as an initial symptom, but cases have been recorded in which the menses continued after signs of the disease were pronounced. Visual disturbance along with impotence is recognised as very suggestive of pituitary tumour, and interference with the visual apparatus occurs in the greater proportion of cases of acromegaly. Exophthalmos has had reference; the eyeball may, however, be rather

hidden by thickened lids and eyebrows. Hertel analysed 175 cases,92 of which presented eye complications. In three-quarters of these the optic nerves were affected,usually with atrophy. (Osler) Bitemporal hemianopia is often an early sign. Contractions,often irregular,of the fields of vision are common: this often more readily detected with colours. Smell and taste may be affected. Cerebral tumour affections,apart from the above,occurring in the course of the affection are headache,vomiting and dizziness. These are distressingly severe in some cases. Convulsions may occur. There may be mental slowness and depression,with loss of memory and lack of energy and of application: other psychoses may arise.

Sensations of burning and of coldness,tingling, numbness and pain,often severe,are experienced by patients in the hands,feet,tongue,and it may be in the trunk and along the limbs. These often abate considerably as the case assumes a chronic nature. Muscular movements are sluggishly performed. The patients are often clumsy. Power is gradually lost, till pronounced weakness may be felt. Movements of the limbs may be impaired by some effusion into the joints,which are at times roughened and creaking,as well as by muscular weakness. Marked alteration of the joints is not characteristic. The affection of the bony system is of marked importance and claims the chief place in some definitions of the

disease: e.g.,in Osler's Principles and Practice of Medicine,1909,where the disease is classed under Vasomotor and Trophic Disorders,it is described as "a dystrophy characterised by abnormal processes of growth,chiefly in the bones of the face and extremities;" and in Keen's Surgery,1907,vol.II,where it is described as "an acquired disease,characterised by peculiar changes in the bony system dependent upon disease of the pituitary body." In the latter work,in discussing the pathology,the writer says the histologic changes are not well understood,and considers them to be largely due to a new deposit of bone by thickened periosteum,while in the marrow there may be evidence of coincident lacunar resorption. The increase in size of the bones of the hands and feet may be shared by the immediately adjacent ends of the long bones. In the typical hand,lengthening is not a distinct feature; but in those cases where it is,there would appear to be increased growth of epiphysis. The bones generally tend to be abnormally massive. The bony sinuses about the skull are expanded to a varying extent; the frontal sinuses often show this. At times the sphenoid cells are invaded by the growth of the tumour. The orbital dimensions may be altered by the expansion of neighbouring sinuses. The changes in the skull demonstrable by radiography are important diagnostic signs -- according to some,the only positive signs of acromegaly(Launois and Gastron,

quoted by Evans)[4]. These changes consist in very irregular thickening of the cranial parietes, which gives rise to a polygonal appearance of the skull. The external tables are separated by an abnormal and irregular space, owing to an alternate separation and approximation of the tables. The post-lambdoidal prominence is exaggerated, and there is more or less marked increase in the antero-posterior dimensions of the pituitary fossa. There is no increase in the area of the palate. This is actually diminished in the acromegalic, especially that of the lower dental arcade. The vault of the hard palate is increased: porous vascular bone is heaped up on the alveolar margin, elevating the dental sockets. The right and left lower molars, in place of being nearer together than the upper, are wider apart and project beyond the upper dental arcade(Keith)[5].

The patient whose case is described below presented herself at the Cumberland Infirmary, Carlisle, on the 11th. June, 1902. She was 43 years of age, engaged in the work of her household, and had been married for 17 years. She was born at Brampton, and at the time of admission had her residence near Keswick, both districts in the County of Cumberland. She complained of:-

(a) Alteration in the form and size of her head and face and extremities, with debility, and difficulty in locomotion.

(b) Swelling in the neck and obstructed breathing.

History of the Present Illness.

In relation to (a), the onset was nine years before -- 1893, at which date her eighth and last confinement took place. The delivery was instrumental, the child being born apnoeic and not surviving. "A good deal of blood" is said to have been lost at this labour. The lochia were scanty, and the return of strength was tardy. The debility persisted, and within a few weeks from her confinement there supervened severe pain in the ears and in and behind the eyeballs. Then, as was remarked by others, the features and limb extremities began to alter. The lower eyelids became thickened and baggy, the face broadened, the ears increased in size, and the lips became large and protruding, while the tongue also definitely enlarged. The hands more especially, but also the feet, became thickened and

broader,acquiring a square and blunt appearance. The alteration in size was apparent on being fitted with new gloves and shoes.

We have some guide to the stages of the processes from the fact that Mrs.B.was twice previously an in-patient,but it is regrettable that only brief notes are available. She was in hospital in July,1897,and Sept,1898. In 1898 she stated that she had been obliged to get two larger sizes of boots between the onset of her illness and that date,and that during that time her hands had been increasing in size,and that her nose and other features had changed to such an extent that old friends failed to recognise her. Her sister stated in 1897 that her face had altered much during the preceding two years. The lips were early affected; but a marked feature of the complaint,from the patient's point of view,was the distinct heat and pain in the tongue,which felt big and troubled the patient so much that in 1898 she consulted a medical man as to the presence of cancer. Headache was an early symptom,starting a little later than the pains in the eyes. She stated in 1897 that the headache prevented sleep,and that it resembled a feeling of weight and oppression in the head,and that it was more or less continuous,though occasionally absent for as long as two days. This cephalalgia had distressed her,though intermittently,ever since, but not greatly during the year prior to admission. It was a prominent symptom in 1897,when it was

noted to be fairly constant,frontal,and vertical in position. Till the year 1902,Mrs.B.was unable to do her household work for some years,but during that year she was able to execute her duties. Her hands are now quite useful. Her chief difficulties are in stooping,and still more so in rising up again after kneeling; also in walking,more especially if she has to step over anything. She used to get "spent" easily and perspire readily,and suffered greatly from "cramps in the legs." In 1898 she is noted as complaining of a frequent feeling of faintness and weakness,and of getting very short of breath on exertion. It is to be observed that then there was no mechanical interference with respiration,as the neck swelling was inconsiderable. Her feet and legs swell at times. This was noted on her two previous occasions of residence in the hospital. This did not occur before the onset of her other symptoms. Her hands used to feel numb and stiff,and were subject to attacks of sweating, but painful sensations have been chiefly manifest in the cephalic extremity — headache,and burning in the tongue,ears and eyes. She has always maintained the power of good sight,but for some time has readily tired when reading. For years she has felt "heavy," has lacked interest in her surroundings,and has experienced failure in the power of attention. In 1897,her friends thought she was getting "slower" mentally. About a year ago,she changed her residence from Low Hesketh to Wythburn,

near Helvellyn, a site of greater elevation. Since then, Mrs.B. has felt stronger, brighter and freer from headache and cramps; which improvement she attributes to the change of abode.

Since her last pregnancy, which occurred when she was 34 years old, there has been complete amenorrhoea.

In relation to the goître, which was first noticed five years before, the size of this remained almost stationary till a few months before admission. During that period the swelling steadily and rapidly increased, and extended laterally. For the last month it has been pressing on the windpipe and causing difficulty in breathing.

Personal Health Record.

Mrs.B. was in service before her marriage. She had measles, scarlet fever and pneumonia when a girl. The appetite has always been good: about five years ago, for some months, it was excessive.

She had "rheumatism" (feverishness and swelling of joints) after her first baby was born. Since her last confinement she has suffered from piles, occasionally bleeding, and it is noted in 1898 that this condition, together with headache, was the reason for her seeking advice during the preceding five years. No other illnesses have been experienced.

Family Health Record.

The father died of "consumption:" the mother, a strong, active woman, died from cancer of the womb, at the age of fifty-three.

There have been two sisters. One died when twenty-one years old, of rheumatic fever; the other, described in 1897 as "not strong", is still alive.

Mrs. B. knows of no relative affected with goître, exophthalmic goître, local or general hypertrophies, or other like morbid conditions.

External Appearances (June, 1902).

In surveying the patient generally, the most striking points are the disproportionately large hands, feet and cephalic extremity. Her expression is difficult to describe. It has not that utter stupidity which we have seen figured in accounts of some cases; nor again the gross brutality. But there has been a blotting out of sexual character, and even of higher human characteristics, and we view a physiognomy which we cannot take as an index of the qualities of the individual. The prevailing "expression of emotion" is one of anxiety, due to the exaggerated furrowing of the countenance, especially in the region of the forehead and eyes; while changes about the mouth add an element of perplexedness to the quality of the expression.

Cephalic Extremity.

The cranium and face both appear enlarged, but particularly the latter. The countenance is a lengthened ellipse, with long diameter vertical and greatest transverse diameter opposite the malar eminences. Prognathism (in the sense of projection of the masticatory apparatus in front of the vertical forehead line) is present, but to a slight degree. "Progeneum," or alveolar prognathism, is not marked. The lower jaw is certainly more affected by enlargement than the upper, that is, there is distinctly not the "type carrée" of Marie, but the "type ovoide." The orbital ridges and frontal eminences are prominent, and the malar regions projecting, so that there lies between, that exaggerated depression which Marie, in his second case, likened to that found in a cow. The regions of the antra of Highmore do not appear unduly prominent. The eyelids are thickened, and puffiness in the orbital regions is decided. The naso-labial, frontal and all natural wrinkles and folds are abnormally marked, the folds being thickened. The nose is considerably lengthened and enormously widened; the alae nasi have been especially affected, and the tip is broadened. The cartilages are thick and increasedly resistant. The ears are large, but are not intrinsically deformed, and are not specially thick, though less easily folded up than normally. The eyes will receive attention later, but here it may be noted that, despite the swelling of the lids, there is

undue exposure of the sclerotic. The lips are very thick,both upper and lower — especially the latter,which is turned down. They are puffy and pouting,and show a small grade of cyanosis. The cutaneous covering of the face has the appearance of redundancy,as if it required bracing up. It is thickened,but is freely moveable,not abnormally tacked down to subjacent tissues. It is not coarse and scaly on the surface,and its colour is uniform. There is considerable thickening (subcutaneous)in the preauricular regions. The appearance of the skin of the face is,as elsewhere, peculiar. It is pale,but not with the pallor of anaemia; there is a dull,dead,lustreless look,with a faint ~~and~~ earthy tinge. The conjunctivae are slightly pallid. The hair is turning grey,and is thick and strong in growth. The cranium is capacious,and the parietal regions projecting. The suture lines are not unduly thickened to the touch. There are no tuberosities or boss-like developments,and there is no gross deformity of the cranium considered by itself. The lower jaw is considerably lengthened and the chin pointed. Mrs.B.is endentulous,and has been so since 1897, when,as a result of their general decay,all the teeth had to be removed. The alveolar processes are consequently atrophied,and the lower jaw has not that massive character it frequently attains in this disease. Its angle is considerably widened: the lengthening from angle to symphysis is

bilaterally symmetrical, and the whole mandible approaches the type of the design by Richer in Souza-Leite's Thesis.

Measurements -- Cephalic Extremity.

Maximum Circumference of Cranium - - 23 inches.

Length -- Glabella to Ext. Occipital Protuberance --

by tape -- 14¼ in.

by callipers - 7 5/8 in.

Breadth --

Callipers { Maximum Interparietal - 6 5/16 in.
Tragus to Tragus - 5⅛ in.

Over vertex - 16 in.

(Tragus to tragus by tape --8 each side.)

Bizygomatic breadth of face -- 5 in.

Nose.

Length (under surface of septum to root) - 2 3/8 in.

Breadth (widest part not compressing alae) - 1 3/16 in.

Lower Jaw (angle to symphysis to angle)

- total by tape -- 9⅛ in.

The carriage of the head is peculiar. The head appears to be sinking between the high shoulders and the prominent clavicles, and the neck seems unduly short and thick, with outstanding head rotators.

The neck is the seat of a large goître.

Circumference -- at level of hyoid = 15 in.

round goître = 16+ in.

Trunk.

There is no definite cervico-dorsal kyphosis. The lumbar curve is scarcely apparent,and the spinal column as a whole is somewhat rigid and is powerful looking. The clavicles are prominent and of great strength,with thick extremities. The ribs are massive; they do not project unduly anteriorly. The ensiform is apparently not much enlarged,and the sternum is not tilted forwards at its lower end. This fact,with the absence of pronounced kyphosis, accounts for the non-existence of the double hump or Punch conformation. The mammae are flaccid and wasted. There is flattening of the sacrum,and the innominate bones are thick,but the prominences of their crests and spines,though well marked,cannot be considered as very abnormal. The thoracic circumference below anterior axillary folds is 35 inches.

Upper Limbs.

The large size of the portion below the wrists forms a contrast with that above,where the somewhat wasted condition of the soft parts accentuates the difference. It may be noted here,however,that the framework of all the limbs is of rather a large build. At the elbow joints there is enlargement, which is but partially due to slight effusion,which occurs from time to time but is not permanent. The lower ends of the forearm bones are distinctly enlarged. The hands are hypertrophied throughout.

They are puffy on the dorsum at times: all wrinkles and skin markings are accentuated,and soft parts obtrusive: The veins on the dorsum are rather prominent. The hands are lengthened,but more particularly broadened and thickened,the carpo-metacarpal regions having a spread-out aspect. The digits share in the lengthening,not so greatly as the proximal parts,however; consequently,they look stumpy and blunt. They are flattened,as are the nails,which are wide,though giving the appearance of being disproportionately small. They shew neither longitudinal nor transverse striation. The normal pink tint is replaced by a duller and slightly cyanotic aspect.

Measurements -- Upper Limb extended.

Circumferences:-

Upper Arm -- 10⅛ in.R.and L.

Elbow Joint - 10 - - - -

Level Styloid Processes -7¼ - - - - -

Hand:

Length(centre of interstyloid line to tip of medius)= 7⅝ in.R. 7 11/16 in.L.

Maximum Circumference = 9⅛ in.R. 9¼ in.L.

Medius: Length 4⅛ in.R. 4⅛in.L.
Circumference middle joint 3 3/16 in.R. 3 in.L.

The Lower Limbs.

The changes are analogous with those described in the upper limbs,and,like those,are symmetrical. The knee-joints are large,owing to

effusion and bony enlargement(femoral),both being factors. The malleolar ends of the leg bones are hypertrophied. The foot is longer than normal: the tarsal region is immensely expanded,and the metatarso-phalangeal area laterally extended; the toes are collectively,but not strikingly magnified. There is some oedema -- like thickening in front of the ankles,non-pitting and intermittently present. The plantar pads at the heel and at the area of the foot are strikingly developed.

Knee joints:Circumferences - R.14½: L.14¼.in.

Malleolar Circumferences - R.10: L.10. in.

Foot:

Length(heel to hallux) -- 9¼ inches.

Circumference(scaphoid level) -10½ inches.

As regards the joints,we have mentioned the changes at the elbow and knees,and may here add that the conditions are painless and that there is general absence of articular grating or crackling.

Muscular System.

There is universal flaccidity and a degree of atrophy,most obvious in the pectoral and sural regions. A slight wasting of the hand interossei is observable. There is no undue myotatic irritability: no fibrillary twitchings and no reaction of degeneration. Muscular action is weak and fatigue readily induced.

Dynamometer:

	Patient.	Normal Females.
R.hand	35	about 60
L.hand	35	about 55

There has apparently, during the progress of the affection, been no excessive strength of muscles prior to waste, as has been recorded in a minority of cases.

Review of Measurements and some Comparisons.

Marie originally had the idea that a normal skull circumference in contrast with facial alteration was a feature of acromegaly. Since then enlargements of the cranium have been observed, e.g., 67c. (Schultze): 63·5, 62·8, 61 centimetres (quoted Sternberg): this patient 58·5c., or 23 inches:* average normal female 21 inches: males 21+ inches.

Length: $14\frac{1}{4}$, compared with normal females $13\frac{1}{4}$.

Transverse over vertex:

16, compared with normal females $14\frac{1}{4}$.

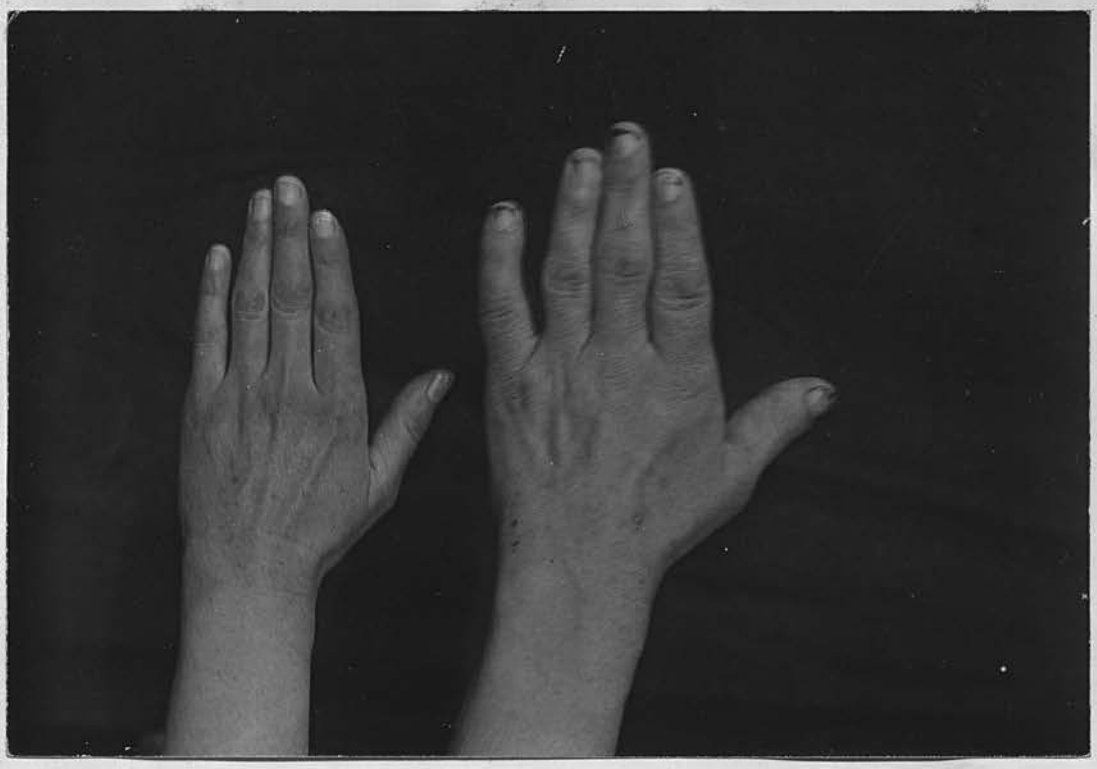
Mandible:

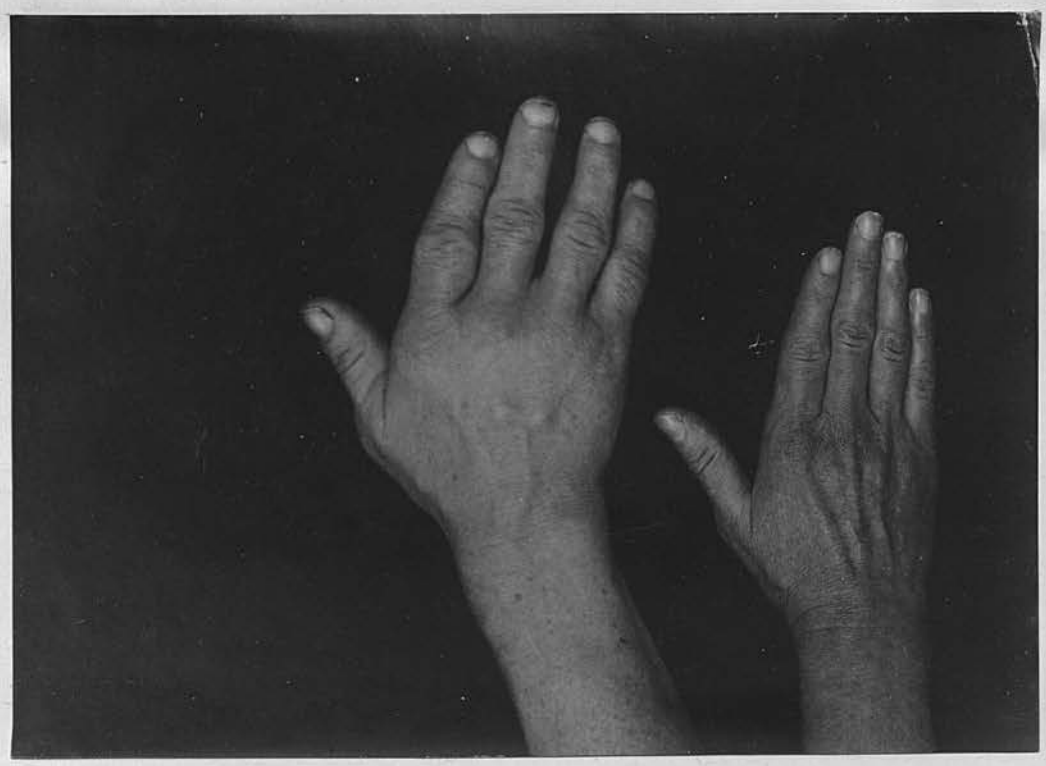
$9\frac{1}{2}$ - - - - - - - - - - - - - - - - $7\frac{3}{4}$

- and in males $8\frac{3}{4}$, $8\frac{2}{5}$ and 9 (male 5ft. 11in. in height).

There is nothing of the "giant" appearance in Mrs.B. which occurs in 20% of these cases (Sternberg), the height of Mrs.B. being 5 ft.5 in. The elbow and knee girths exceed even those of

*Precisely the same as independently taken measure in July 1897, i.e., five years previously.





Hands of patient compared with hands of normal female of similar build

males of average and even large physique, e.g., elbows 10 compared with $9\frac{1}{4}, 9\frac{1}{2}, 9\frac{3}{4}$, and more markedly knees -- $14\frac{1}{4}$ ---------- $13\frac{1}{4}, 13\frac{1}{4}, 13\frac{1}{2}$.

Malleolar Circumferences:

10 --- $9\frac{1}{2}$(average normal female): males $9\frac{1}{2}$(average): 10(height 5ft.11 in.): $10\frac{3}{5}$(diabetic of average height).

Length of Foot:

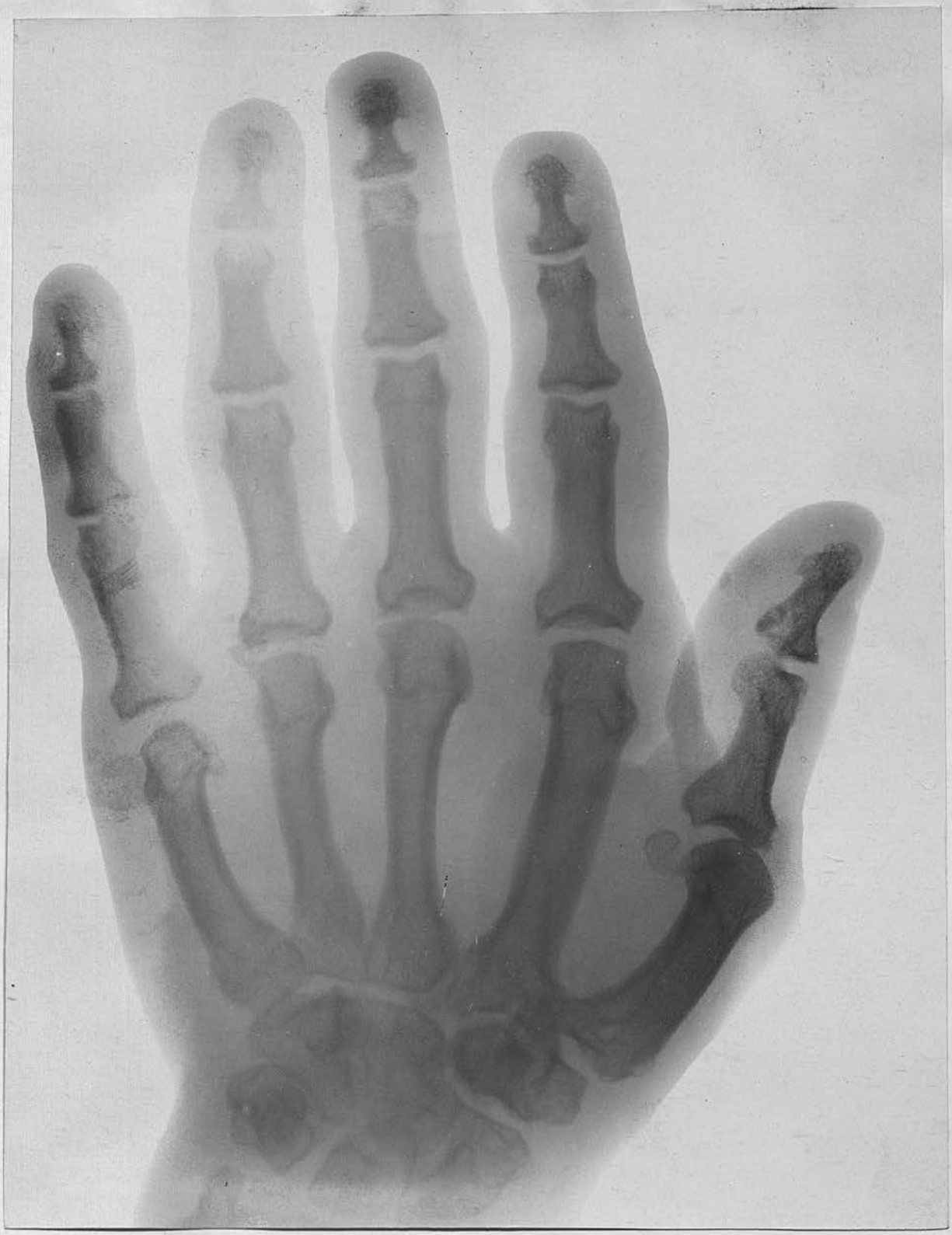
$9\frac{1}{4}$ --- 9 (average female); $9\frac{3}{4}$-$10\frac{1}{4}$(male).

Circumference of Foot:

$10\frac{1}{2}$ ----- 9(average female), $9\frac{1}{2}$(average male), 10 in.(in above diabetic).

The hand measurements are striking to a sufficient degree, and the aberration in growth is apparent in the comparative photographic representations. The length is that of a tall man's hand($7\frac{5}{8}$-$7\frac{3}{4}$): the circumference much greater ($9\frac{1}{4}$-$8\frac{1}{4}$).

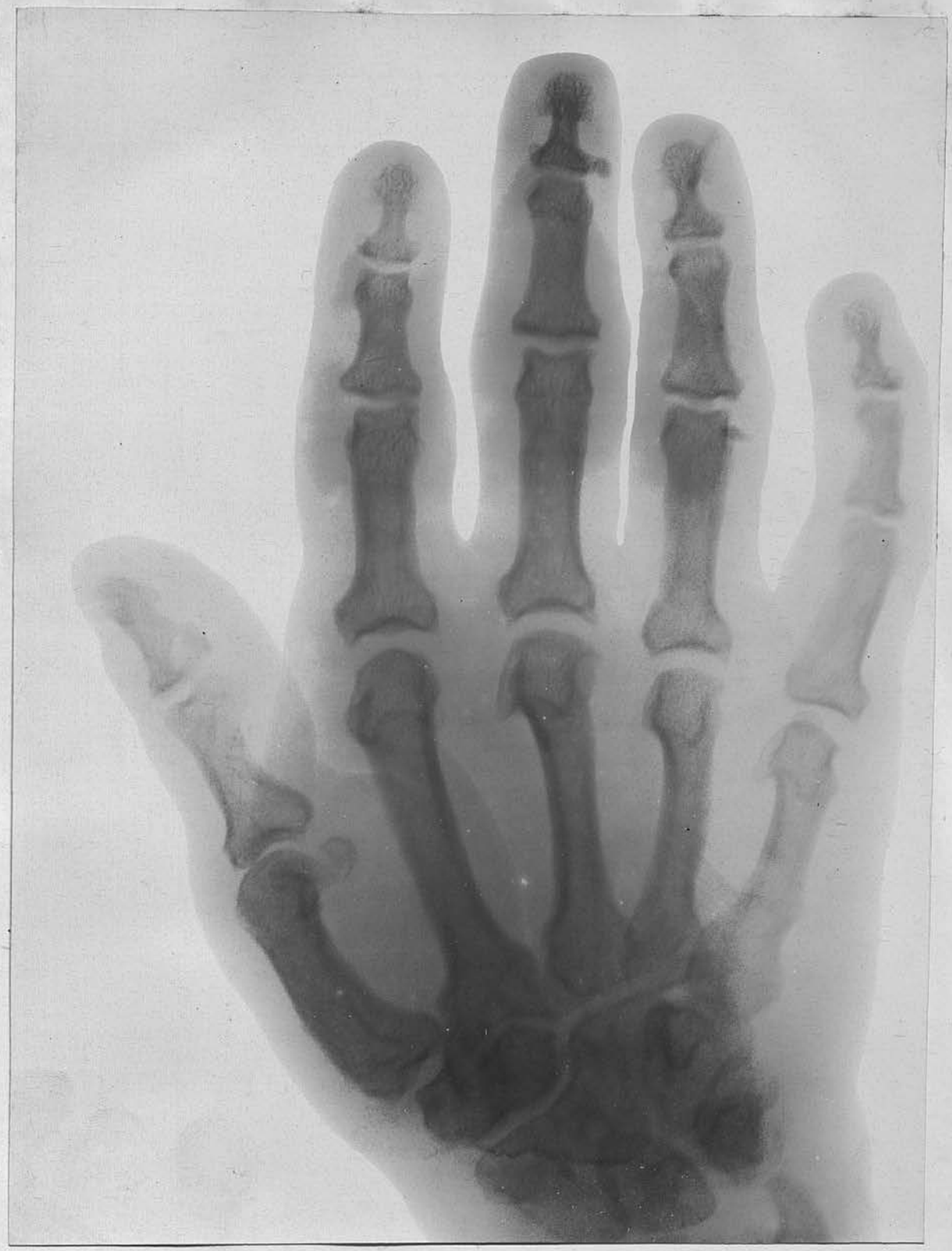
As demonstrating the particular segments affected specially, we may refer to a case of Hypertrophic Pulmonary Osteo-Arthropathy for comparison. In a recently reported case (6) of a male, the styloid circumference was $7\frac{3}{4}$(Mrs.B.$7\frac{1}{4}$), while the metacarpophalangeal circumference was $8\frac{1}{2}$, which, though a large measure, is much behind that in Mrs.B. --$9\frac{1}{4}$. It is this involvement of the middle segment of the hand, as well as of the distal digital segment and the proximal segment at the wrist, which justifies the description of "main-en-battoir." Though there is considerable elongation of the hand, its type is not "en long" or "type géant"; but, if one



must adjust it to Marie's distinction, it certainly belongs to the "type passif."

Radiographs.

These bring out some interesting points. The increased size is due to changes both in the skeletal and in the superimposed structures. As expected in the massive form, the bones generally are thickened. The bones of the carpus are large, with somewhat increased irregularities, and ligamentous and tendinous attachments are pronounced --witness the unciform hook. The shafts of the metacarpals are bulky, especially those of the pollex and index. Their extremities are likewise thick, with exaggerated roughnesses. The phalanges show changes of like nature and of slightly more pronounced degree, and their appearance suggests diffuse increased growth of the diaphyses, periosteal in origin, as described by Boltz. The terminal phalanges exhibit a state which has been described as present in acromegaly, viz., the cluster of small projections at each distal extremity. Sternberg emphatically states that the condition is to be seen in very many normal hands. As a rule, when marked, the appearance resembles that of a bunch of mulberries, and not commonly, as in this case, are the terminal phalanges like sheaves of corn, with overhanging fringes. This, of course, is not a feature solely characteristic of this affection, but is, we consider, well illustrative of the tendency to exaggeration of the normal coarseness of



surfaces of attachment. The intermetacarpal intervals are evidently great. This change is brought about by the presence of the enlarging intervening soft parts, according to Sternberg, but it may also be due to expansion of the bases and of the carpal arch, the increase in the soft tissues being concomitant. There does certainly appear to be an increase of distance at the interphalangeal and metacarpo-phalangeal lines between opposed bone extremities. Thickening of cartilage has been suggested by Schlesinger as an explanation of this appearance noted by him and others. The increase of the articular interval may have been brought about by the mechanical difficulties arising from irregularity of the bony ends, or the apparent separation of the ends be due to a laxity of the joint capsule. As noted, the length of the hands has been considerably augmented, and this we may attribute to participation of the epiphyses. Cepeda has noted lengthening of epiphyses, and new osseous formation in the position of cartilage has been observed (Klebs -- Marie --Marinesco). Holst, more particularly in regard to the "type géant", pointed out the occurrence of elongation of the hand long bones. Doubtless, in this particular case, general amplification of the carpus is a factor.

Integumentary System.

In addition to what has been previously stated concerning the skin and its appendages,we may say that there is nothing of the nature of molluscum fibrosum,verrucae,or xanthoma. There is no beard or other unusual distribution or growth of hair. There are no areas of abnormal pigmentation. Perspiration is not so marked as formerly.

What certainly does obtrude upon one's senses is a very offensive odour about the patient. This is not always present,and probably varies with the temperature and with the activity of the skin glands There is no foul discharge,and Mrs.B.is a cleanly person. The presence of the smell has been repeatedly confirmed by nurses and others. Such offensive smell has been noted in an acromegalic negress,by Berkeley,but its occurrence in that instance is,judging from personal experience of the variety of offensive odours exhaling from individuals of that race,perhaps less extraordinary.

Circulatory System.

Symptoms arising in connection with the circulation have been mentioned in the history. There has been considerable amelioration of them during the past twelve months. Physical examination suggests the presence of cardiac enlargement of slight degree. There are no murmurs: the quality of the sounds is not indicative of hypertrophy,and the events of the cardiac cycle are in normal relationship. There is no pulsation in the neck or other

abnormal situation. The pulses in both radials are equal and very large: regularity in rhythm and force is observed. The vessels are assuredly much increased in thickness and calibre,but apparently lumen and wall are in proportion. The radial arteries,in fact,are developed correspondingly with the hands. The tension is rather low. There is slight varicosity of the veins on the tibial aspect of each leg.

Pulse Rate.

This at present varies from 84 to 90 per minute. In 1897 she suffered from a degree of tachycardia: the rate on Aug.11th.was 96. This rose to 130 on the exhibition of Thyroid Extract and returned to 96 on discontinuing the drug.

Respiratory System: Thyroid Gland.

There is noisy stridor,owing to pressure exercised by the goître on the trachea. The presence of a "small goître" was recorded in 1897. In October,1898,the neck measured 14¼ in.; it is now 16 inches over the goître. This is situated bilaterally in anterior and posterior triangles of the neck. There is no evident pulsation within it. External examination of the larynx is prevented by it. In 1897,"no laryngeal enlargement" is recorded. There has been no epistaxis. Pulmonary resonance encroaches upon the normal area of cardiac dulness; but for this(of slight degree),there is no discernible change in the organs. There is no cup-shaped area of dulness at the upper part of the sternum.

The rate of respiration is 22. The range of thoracic movement is limited. The chest circumference is not large, this because of the wasting of superjacent soft structures. The ribs individually are certainly massive.

Alimentary System.

The appetite is moderate. Constipation is troublesome, and bleeding from haemorrhoids is recorded. A slight amount of dysphagia is present, from pressure by the thyroid. The tongue is immense -- broad and thick. Its large size is a hindrance to mastication and speech. Its surface is not greatly changed. It does not continually project. No distinct thickening is observable of the pharyngeal and buccal lining which, in other cases, has occasionally been so thick as to hang in folds (Naunyn). There is no evidence of dilatation, enlargement or diminution of any of the abdominal organs. There is total absence of any suggestion of "splanchno-megaly" in the abdomen.

Urine: Nutrition.

During Mrs.B's. stay in hospital, from June 11 to Aug.8(1902), before and after partial thyroidectomy(performed June 16), there was neither albuminuria nor glycosuria. The specific gravity was normal in range. The quantity in 24 hours was rather small --about 25 ounces. The reaction was normal. Phosphaturia was not constant. When she was admitted in July 1897, the presence of sugar was noted. The patient at that time had also polydipsia --

there was no albumen present. A little later(in August),but still before thyroid was exhibited,the quantity of urine in 24 hours was 20 ounces,i.e., less than a normal amount,which circumstance,however,may attend hunger and thirst. In 1898 there is no record of sugar in the urine. In September of that year the appetite was noted as "rather ravenous." The patient remembers that about that time she used to be "dreadfully hungry,"even within a brief space of time from meals. Soon afterwards the appetite became normally good and remained so during her stay in 1898. The weight in 1902 was 9 st.4 lbs.: the temperature subnormal.

Reproductive System.

The patient has had eight children,all stillborn except one boy,how eleven years old and healthy. All the labours were tedious,several instrumental --always "a good deal of bleeding." There was one miscarriage of a pregnancy about the middle of the series. The dead-born children were full time and were felt alive just before birth. Thus there were nine pregnancies and eight full-time labours in the space of between eight and nine years. Mrs.B.always "lost a great deal with her courses", which started rather late,the exact age not being known. Persistent amenorrhoea since her last confinement has been noted. In 1898 "milk in the breasts" is recorded with the history of presence of secretion ever since the last

confinement. In 1897 mammary secretion and ovarian tenderness appear to have been noticeable, though not every day. There was no secretion in the breasts in 1902 or subsequently. The external genitals, vagina, uterus and annexa reveal nothing of abnormal character on physical examination.

Ductless Glands.

To the thyroid gland reference has been made. No lymphatic glandular enlargement is noted.

Blood.

As with previous cases, no striking change is observed. In drop, the appearance is normal, and coagulation time is the same. In film, the red cells are well formed and of uniform size, but show slight deficiency of colour. No abnormal forms are present. There is slight and inconstant leucocytosis. Relative proportions of white cells are within normal limits. Red cells 3,500,000+. Hb. 60%.

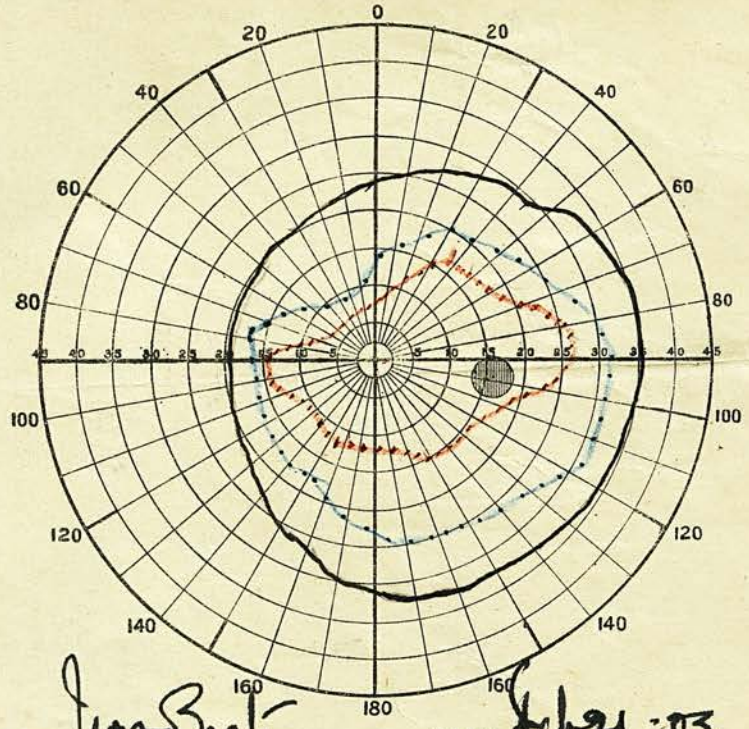
Nervous System.

The demeanour of Mrs.B. is placid. She is apathetic and will retain one attitude long at a time. She is, though seldom, emotional. Except for this trait, she is a matter-of-fact, intelligent person. Attention and concentration are impaired. Depression of spirits to a moderate degree is observable. She does not sleep well, and has not done so for some years; nevertheless drowsiness is almost always experienced.

Paraesthesiae have largely passed off —

the acro-paraesthesiae in the tongue and ears have entirely ceased to trouble. The hands feel "peculiar and stiff" occasionally. Sensibility to touch, pain and warmth are universally present, though registration of stimuli is a little delayed. The muscular sense is accurate. Motor power is weakened. The gait is inelastic and the bearing listless. There is no ataxia. Romberg's sign is not present. There is no tremor. "Cramps in the legs" trouble the patient. The knee-jerks are present, but certainly diminished. Superficial reflexes are elicited, but are not active. Speech is slow, and is thick from the lingual alteration. The voice is monotonous and deep. Organic reflexes are normal. Taste and smell are not appreciably altered. The sense of vision has suffered, the sight apparatus having been considerably involved in the morbid processes.
As regards external appearances, some differences were noted between observations taken in June 1902 and in March 1903, respectively. At the former date there was much swelling about the lids, the eyes were somewhat staring and proptosed, and the upper lids hung back in associated downward movement with the globes. (This last condition was noted in 1897.)
In March 1903, however, the swelling had subsided, also the "staring" aspect and the proptosis had lessened. A comparison of the photographs will demonstrate these remarks. At the latter date, an examination

RIGHT EYE.



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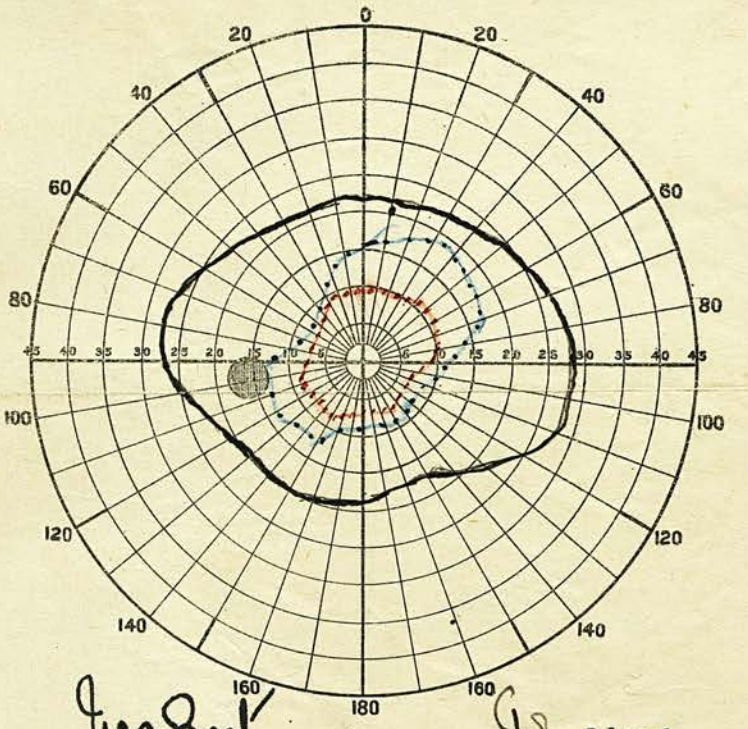
LEFT EYE.



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conducted in conjunction with Dr.Hill of Carlisle resulted in the following report:-

There is slight exophthalmos,but no difficulty in closing the lids. The pupil reflexes are rather sluggish,though there is response both to light and to accommodation. The visual acuity is $\frac{6}{36}$,but patient can be brought to read some of the letters at $\frac{6}{24}$ by turning head to right and reading with left eye. The tension of both eyes is normal. The ophthalmoscope shows the right disc to be paler than normal: the left is distinctly atrophic in its outer half. The vessels are contracted in both eyes. The paler half of the left disc shows a refractive measurement of +0,while the nasal half is 1 D. The right eye was hypermetropic about 1 dioptre. The fields of vision show more or less concentric contraction,which is more marked when colours are used,the field in the case of green not extending beyond ten degrees in any direction.

On June 16th.1902,partial thyroidectomy was performed. Access was obtained by a long incision, obliquely directed from the right side above to the left below,over the swelling,and ending just above the left clavicle. The portion lying to the left of,and pressing against,the trachea was removed after dislocation of the mass and ligation of the pedicle. The appearance and behaviour of the skin on section were as usual. The trachea was slightly deflected to the right. There was

very free haemorrhage from various radicles in the left supraclavicular region,probably as a result of abruptly changed pressure. In this connection,it may be recalled that several observers (Cunningham,Klebs,Claus,V.d.Stricht) noted post mortem in other cases an extraordinary amount of blood in the veins. The anaesthetic (chloroform) was well borne. The portion of thyroid removed showed,on the right, an old-standing degenerated fibrous and cretaceous condition; elsewhere the gland was,in places, cystic,and in places quite normal. The cysts contained colloid material,and a few contained blood. Briefly put,the appearances were precisely those of simple goîtres examined by us, removed from patients with chronically enlarged thyroid glands. We are informed by Dr.Lediard that Professor Greenfield,who examined the specimen,also reported to that effect.

Her progress subsequent to operation was uneventful. Her pulse was increased in frequency to 100 per minute for a week; it then settled down to 90,at which it remained during her two months' continuance in hospital. The respiratory embarrassment had been removed. During this time thyroid extract (gr.V bis in die) was exhibited and was well taken. On a few occasions headaches were very severe,with accompanying depression of spirits. For these

A

Phenacetin(gr.X) was of benefit; Ergot (liquid extract ℥ XV t.d.s.) seemed also to ameliorate the symptom. In 1897 Bromides and Iodides, and in 1898 Bromides and Belladonna were tried for that symptom,and seem to have procured her relief,in conjunction with general measures. After her discharge (Sept.8,1902) the thyroid treatment was discontinued. A few weeks subsequently,Mrs.B.was seen by her doctor outside, and was suffering from "a congestive attack of the thyroid,"the gland being as large as it was prior to operation,and causing great distress and anxiety. This swelling subsided within a few days,and,after that,there was apparently a steady shrinkage of the mass,so that when she was re-admitted for examination in February 1903 the neck circumference was 13 inches,instead of 16 inches as before operation. The right or untouched side of the goître had shared in the shrinkage. This is not uncommon after goître operations. During the intervening period,too, general changes occurred. Those in connection with the eyes,e.g.,diminution of lid swelling and of proptosis,have been mentioned. The face in general had altered in great measure,and offered that shrunken appearance which Duchesnau pointed out may obtain,where,with prominent lips and malars,we have non-dilatation of the maxillary antra,but which,in this case,only became apparent after loss of cutaneous swelling and after wasting of fat and connective tissue had

B.

Photographs A and B show shrunken appearance despite increase of weight

set in. Subsidence of the pre-auricular thickening, previously noted, was decided. This decrease in subcutaneous padding was observable everywhere, and is shown in the photographs taken on the different occasions. The maximum hand circumferences were slightly less (by $\frac{1}{8}$ in.). The muscular wasting, especially about the legs, had progressed. Despite this, the body weight had increased from 9 st. 4 lbs. to 9 st. 9 lbs., which presumably indicates that the internal organs or skeleton, or both, were heavier. Mrs. B. expressed herself as feeling improved, but she appeared somewhat weaker.

Discussion of Case.

From the foregoing,we conclude that the case is one of that condition described by Marie under the name Acromegalia. The outstanding signs — large extremities — are present,and,in association,many of those symptoms recognised then and now as characteristic of acromegalia. The case is,as are the greater number,of the chronic variety,having a duration of over nine years,reckoning from the onset of the amenorrhoea, which Souza-Leite considered as determining the initial period. The age at onset (34 years) is greater than is most usual. An important majority commence between 19 and 26(Souza-Leite): the period of greatest frequency is between 20 and 26 years(Guinon);while of 70 cases in women, Sternberg found that 50 per cent occurred at ages between 21 and 30, and 25-7 per cent between 31 and 40 years. Statistics are also given by him relating to the onset of amenorrhoea,which correspond in the main with the above,thus corroborating Souza-Leite. It is worth observing that in Cattle's case (7) the health began to fail three years before amenorrhoea was established,and that "out-patient notes" include the observation "face somewhat acromegalic" two years before the menses stopped. The present case may be classed with six collected by Sternberg,where the menses,having failed to appear owing to impregnation,have not

returned after delivery. As in all preceding cases of the sort recorded, there has been no conception since acromegaly and amenorrhoea commenced, showing that with the latter there has been disturbance of ovulation. A very interesting case, unique in the literature, has been recently recorded, (8) where pronounced symptoms of acromegaly arose during gestation and subsided rapidly after delivery. These occurred in a primipara, aged 26 years, with no history of previous menstrual or other disorder of importance. Though there was manifest pituitary disturbance in this case, we note the absence of definite signs of tumour; so the subsidence of the acromegalian disturbance is the more credible. This appears to be a solitary instance, of which we have knowledge, of acromegaly associated with pregnancy disappearing in the puerperium.

Headache has throughout occupied a prominent place among Mrs.B's.symptoms. This it was for which the woman Fusch, Marie's first case, sought advice at Charcot's outpatient department. Vomiting, another tumour symptom, has not been present in this case. The painful sensations experienced during the progress in the affected parts (e.g., the ears and tongue) ceased, as is common, after these changes were established. Glycosuria was likewise not a persisting phenomenon: this is often temporary, and associated, as here, with excessive hunger and thirst. In the external appearance of the patient, we have a good picture of a well-advanced example of the

chronic type. What is atypical is the absence of kyphosis and accompanying thoracic deformity. Souza-Leite classed deviations of the spine, principally in the upper half, among "the constant objective symptoms." But Sternberg quotes eight pronounced cases where these were not evident, and to them may be added an acute case published by Mitchell Stevens.(9) The insufficiency of cardiac action evinced in Mrs.B. by dyspnoea, faintness and slight cyanosis has been frequently described in other instances of the disease. Pronounced heart change as following vascular alterations is not evident, and, judging from the radials, we would say that the narrowing of the lumen from thickening of the artery wall has not occurred. Fritsche and Klebs laid stress on the diametrical increase in the vessels witnessed P.M. by them in the case of Peter Rhymer. We have noted the absence of dulness over the upper part of the sternum described by Erb: this absence would appear to obtain in the majority of instances.

Mental changes are not profound, relatively to what occurs in e.g. Myxoedema. We have in Mrs.B. the symptom of somnolence, of which complaint has been made by a majority of acromegalic persons, notably the case (III in Marie's first series) originally published by Salcerotte-Noël, where it was attributed by Salcerotte to "compression of the brain by the thickening of the skull."

The tendon reflexes have usually been found normal or increased: absence or decrease (as in this case) has been recorded. The incidence of failure

of muscular power and of wasting without the reaction of degeneration has been demonstrable in this case. It is a feature of great constancy, and has been regularly recorded since the early days of the "Sieur Mirbeck" case (1772), where the phenomenon was tersely described by Sancerotte-Noël in the phrase, "His bones appear to have become thickened at the expense of his muscles."

Considering the visual organs, we know that the degree of proptosis of the ocular globes is liable to variations, and may diminish, as in this case. Exophthalmos is not the rule, but has been recorded from time to time. Case XXXIII in Souza-Leite's series was originally described by Lancereaux as "exophthalmic cachexia." The classic sign -- (Schultze's) -- "bitemporal hemiopia" has not obtained in Mrs.B's.case: we have what is frequent, a fairly general limitation of the fields of vision from optic nerve lesion. It is to be noted that these changes are not to be regarded as distinctively acromegalian apart from their significance as pituitary affection. This case, in that she entered hospital seeking relief from goître pressure, is somewhat analogous to Godlee's case.* (10) In this, the patient (a female of about the same age --41 years) had a goître the

* The pituitary body from this case was exhibited by Lawrence on Nov.2, 1897, before the Pathol.Soc.Lond. The gland was the size of a cherry, the anterior lobe only being involved. "The change was not hypertrophic or adenomatous, nor was there any distinct tumour."

duration of which was nine years,and for five years amenorrhoea had existed. With the disappearance of the menses and their continued absence,there were, as generally,progressive changes in the extremities, but in addition a concomitant gradual increase in the thyroid. In the present case the thyroid changes had only greatly evidenced themselves subsequently to the establishment of the acromegaly,and indeed after considerable amelioration of the general symptoms had been experienced.

Aetiological Considerations.

The points in the case with an apparent bearing on these are the disturbance of the genital glands,with the history of the numerous,rapidly repeated pregnancies: the thyroid disease and the manifestations of pituitary affection with skeletal and other,including vascular,changes. The organs with internal secretion would appear to be linked up in function. In this disease the hypophysis cerebri stands in a central,dominating and controlling position,reacting to the stimuli of changes in other glands,but in its response producing the characteristic clinical entity. From the evidence of Marek's case,it would seem that this can be produced by a mere temporary disturbance of balance between internal secretions,and need not necessarily imply grave and persistent structural alteration in the pituitary body. The functional disturbance, however,is almost invariably accompanied by this structural change,which is of the nature of an overgrowth of glandular structure of the anterior part of the organ. There is hyper-secretion by this part. The overgrowth results in an adenomatous tumour,the cells of which originate in the normal cells of the gland and are eosinophile(Fischer). There does not appear to be in the literature of the subject a single case of indubitable acromegaly in which the specific change in the anterior part of the pituitary body was not present. Fischer also maintains that most recorded cases of acromegaly without

tumour of the pituitary body can be shown to be cases of syringo-myelia or gigantism, or more rarely of some other disease.(11) As bearing on this, it is worth noting that there is a skeleton of a non-acromegalic giant in the London Hospital Museum, which, as recorded by Keith, measures 2170 m.m. (7ft. 2 in.) and the pituitary fossa is only slightly enlarged, measuring 15 X 18 X 6 m.m. In the light of other observations, this position of Fischer cannot be considered absolutely unassailable. The difficulties in accepting the view of the necessary presence of a tumour have caused various attempts at explanation of its absence. Tamburini's hypothesis, that the organ, at first hyper-functional, and enlarged, passes later into an hypo-functional state, is one of these attempts. The occurrence of myxoedema following exophthalmic goître is regarded as analogous, the corresponding thyroid changes taking place. With regard to the cases where pituitary tumour has been found <u>without</u> the symptoms of acromegaly, this may be explained on the ground of the close relationship between the pituitary and other glands with an internal secretion. They may counteract it when over-acting, or assume its function when it is removed. Tamburini has explained these cases by the suggestion that death has occurred before the slower skeletal changes could be induced, or that the hyper-functional activity cannot cause

the characteristic changes of acromegaly if it occurs before the age at which the epiphyseal cartilages are ossified.

The presence of tumour without acromegaly or its absence with acromegaly may be considered ~~may be considered~~ from another side. In consideration of the function of the thyroid, we have to reckon on the presence of accessory bodies or parathyroids. It appears, too, that there are good grounds for having to adopt this attitude with regard to the hypophysis. Eidheim reported a case of acromegaly with apparently normal pituitary, where a tumour composed of hypophyseal tissue occupied a recess in the sphenoid bone, where it had apparently developed from a primitive nest of hypophyseal tissue in connection with the cranio-pharyngeal canal. Levi has demonstrated the persistence of this canal in two acromegalic skulls. (12) It appears that accessory pituitary bodies are normally present in the naso-pharyngeal vault. Killian and Eidheim noticed tissue of this nature in this situation in new-born children. Engel and others have described cases where the hypophysis was situated in the cranio-pharyngeal canal, not in the sella turcica. In 1907 Harnijro Arai extended the researches of Eidheim and Haberfeld and classified accessory hypophyses into 3 groups:

(1) Accessory cranial hypophyses.

(2) Hypophyses situated in the cranio-pharyngeal canal.

(3)Pharyngeal hypophyses of Eidheim.

As a result of later publications by Civalleri (1907) and Haberfeld (1909),we know that accessory hypophyseal tissue is normally present in adults of any age,as well as in foetuses and the new-born: that this tissue is histologically of the same structure as that of the normal anterior lobe of the pituitary,though according to Haberfeld the chromatophil cells are in relative excess and other cells are sometimes absent.(13) The pituitary defects may in some cases date back to developmental errors,occurring in or about the second month of foetal life,in connection with the primitive peduncle.

These points tell against the theory of Marie that acromegaly is a dystrophy of deprivation or of lowered function,and seem likely,when they are investigated in ~~connection~~ regard to actual cases of the disease,to strengthen the view that there is hyper-function of the hypophysis.

When we come to consider the rôle of the pituitary body,we find facts supported by many anatomical,experimental and surgical observations. The pituitary body is not a rudimentary organ. The sudden removal of the anterior part of the gland is incompatible with lengthened maintenance of life(Cushing). Total extirpation led to death(Paulesco,see Cushing). The posterior part, composed partly of nerve fibres and cells,

exercises a powerful influence over the vaso-motor nervous system (14) and the regulation of the blood-pressure, especially in the brain; while the anterior part, which is glandular, influences the development of the form and size of the body and the growth of the bones (Fischer). The pituitary acts in conjunction with the thyroid, in guarding the brain against undue congestion, in its capacity as an auto-regulator of the intra-cranial blood-pressure (Von Cyon) (15). It has a chemical as well as a mechanical function. Von Cyon finds that the glandular portion manufactures two substances, the more important of which he names "hypophysin." This has the power of increasing the heart's action and of raising the blood-pressure in accordance with the views of Schäfer. Von Cyon records diminution of pulse-rate, with an increase of strength after the intravenous injection of pituitary extract and considers this an important action. "Hypophysin", like Iodothyrin, is a powerful antagonist to the action of atropin and nicotin on the vagus (V. Cyon). The pituitary influences not only the sympathetic and vagus nerves, but also the metabolism of the tissues and glandular secretion. Extracts of the infundibulum also cause contraction of non-striped muscle, such as that of the uterus, intestine and dilator pupillae, and contraction of the coronary arteries. Harvey has shown, in his work at Cambridge, that pituitary extract caused marked hypertrophy of the heart

and had a smaller effect on other tissues,when administered to rabbits. This cardiac hypertrophy is a common feature of acromegaly. Humphry and Dixon (loc.cit.) made separate extracts from the anterior and posterior lobes of the pituitary,40 hours after death,and found"not a trace of pressor substance." "The presence of pressor substances could,however,be determined readily enough in other tissues."

In spite of their difference in origin and structure,and apparently even in function,the anterior and posterior parts of the pituitary appear to have some important connection functionally. Impotence, with atrophy of the testes or ovaries,with sometimes obesity,occurring in acromegaly,is not caused directly by the over-functioning of the glandular part of the pituitary,but by pressure exercised by its enlargement on the nervous part of the organ. Disturbances of this part of the organ may be followed by those results,as shown by experiment and by surgical observations.(Fischer)
(16)

Keith has brought forward evidence that suggests that at least one of the substances secreted by the anterior part of the pituitary is of the nature of a hormone. This renders the osteoblasts hypersensitive to the various stresses which fall on the human skeleton during life. He thus explains the increased growth of bone at muscular attachments,at parts of bones exposed to repeated pressure or tension. If the epiphyseal lines,

the osteoblasts of which appear to be especially affected, are still open, gigantism is produced. In acromegaly, the architectural function of the osteoblasts is not lost; new bone is laid down to meet the pressures and tensions exerted upon the skeleton. In normal individuals the osteoblasts have almost ceased to react to these stimuli after 25 years of age, but in acromegaly they are rendered so sensitive that they react to stimuli which in the normal would be ineffective. The normal coördination between bone formation and bone absorption in growth processes is in acromegaly lost to a certain degree; in the later stages the absorption may be the more marked. The pituitary is functionally connected with this coördination during the growth of the skeleton. In acromegaly, an imperfect process of growth, is again awakened. The new deposit of osseous matter does not depend, apparently, on the pituitary secretion. Osteoblasts may be stimulated to lay down newbone in many ways, and in acromegaly they appear to respond more readily than normally. The changes represent exaggerations of the normal processes of growth. The key to them in acromegaly is to be found by studying the successive changes in the crania of growing anthropoids, best realised in gorillas, from which it is seen that the alterations in the acromegalic skull are very closely of the same nature as are the changes in the skeleton elsewhere. Wherever there is traction applied by

ligaments or by muscles,or pressure applied as in standing or walking,growth takes place where the various forces act,e.g.,the extension of the boundaries of the temporal fossa,the supra-orbital ridge projection,and the mandibular alterations.

Atrophy is also at work(correlation of absorption with growth),e.g.,in the bodies of the vertebrae,the tarsus and the mandible,causing kyphosis, flat-foot and (in part) the widened angle of the inferior maxilla. From what is known of the function of the pituitary,it appears that these changes,comparable in acromegalics,anthropoids and Neanderthal man,are all due to hyper-pituitarism,as distinguished from hypo-pituitarism,where the pituitary secretion is much below normal. As to what stimulates the pituitary to over-secretion,we know of some conditions which do so. Pregnancy does this; so do castration and thyroidectomy; and correlated with the excess of function,we get the effect upon growth.(17) As the growth of bone implies active formation of vessels,we get in acromegaly special affection of the vascular system of the bones.

In contrast with acromegaly,considered as a condition of hyper-pituitarism,we have certain conditions pointing to lowered pituitary action. Von Eiselberg(18) says: " It seems to be an established fact that a pathological increase of the function of the anterior portion of the hypophysis produces hyper-pituitarism,i.e.,gigantism in youth,acromegaly in

adults; while a diminished function produces hypopituitarism,i.e.,a rapid deposit of fat in the subcutaneous tissue,a persistence of a juvenile type in younger individuals,and a decrease or loss of genital function in the adult.(19) The diagnosis of hypopituitarism(Frőhlich's syndrome) is based on general cerebral symptoms,changes in the optic nerve,and an adipose-genital degeneration. Occasionally abnormal temperature,drowsiness and polyuria."

As a further illustration,we have the condition designated by Hastings Gilford as ateliosis. Also in this category may be the excessive adiposity of the menopause,diabetes in fat people and after skull injuries,adiposis dolorosa,cretinism and achondroplasia.(20) According to Hastings Gilford, we have in ateliosis -- childish facial appearance, diminutive stature with short,small extremities, delicate soft skin,thin piping voice,small bones with ill-developed muscular prominences,diminutive jaw-bones with incompletely erupted teeth,diminished urinary secretion,impaired appetite,low arterial tension and slow pulse. The development shows a remarkably retarded rate of progress. There is delay or absence of union of the epiphysis to the diaphysis,and the teeth may not be erupted even at 50 years of age. The fontanelles,the position of the testicles,and the development of the sexual organs show the retardation or arrest of normal growth,and may even indicate the date of onset of the process,which may occur during fetal life,

during infancy or early childhood,or during the period between then and puberty. There is lack or absence of hair on the face and covered parts, though the head may have a fair amount. In Fröhlich's syndrome we have a similar condition, except that it may affect adults as well as persons before puberty,and that the deposit of excessive subcutaneous fat and somnolence are pronounced symptoms. The skin also is apt to become coarse. Mild symptoms of myxoedema or acromegaly may be associated with symptoms of pituitary insufficiency. Cases occur in which the latter symptoms are associated with those of hyperpituitarism,and vice-versa. In both conditions also it is to be noted that the symptoms may be modified by the influence of other glands with internal secretions; so that it may be difficult to class a case as an example of over- or under-pituitary action.

Amongst conditions which may be associated with pituitary disturbance, there are pregnancy, castration,and thyroid alterations,including thyroidectomy. Thyroidectomy,castration and pregnancy are considered by Keith to be known to stimulate pituitary secretion. Judging from the closely associated functions of the thyroid and pituitary and the frequency of thyroid change in pregnancy, it is not surprising that pituitary function should be affected. Just as thyroid influence may be disturbed with loss of secretional balance in the body chemistry and with resulting toxaemia

in pregnancy, so may pituitary effects be manifested during the same state, in some cases these effects displaying the signs of acromegaly. In this connection, too, the occurrence of "goître puerperal" is of interest. There are on record cases of the appearance of bronchocele after confinement, its subsequent disappearance and reappearances with successive labours, and its ultimate establishment.(21) So that on similar lines we may eventually get the establishment of pituitary structural change. Many writers have recorded the occurrence of congenital goître following the administration of chlorate of potash throughout pregnancy in non-goitrous, multiparous women, with no history of syphilis nor of having previously borne children with goître(22) (Simpson, J.Y. and A.R., Hewetson, Macdonald, Fothergill, etc.). These facts open the way to a suggestion of a toxaemic origin of the pituitary change as of the thyroid change.

Enlargement of the hypophysis after thyroidectomy was amongst the earlier laboratory observations (Rogowitsch, Gley and Hofmeister and others), and suggested some compensatory action, and, though this could not be definitely established, certainly indicated inter-dependence of action. The thyroid gland is seldom found normal in acromegaly (5 out of 24 in Furnivall's series).(23) The pituitary body in cretinism and myxoedema,

the observations on which by Boyce and Beadles and others are well known,frequently shows associated changes. Cretinism by many is now put in the category of hypo-pituitarism. Myxoedematous appearances have,however,been frequently noted in cases of acromegaly. The thyroid has been observed to figure in acromegaly in a somewhat special manner as a phenomenon in Graves' syndrome,the signs of which are at times included in the picture of the case. Murray has directed attention to the possible coexistence of the syndromes. He records two cases,and three others are mentioned (by Lancereaux). Cattle's case (loc.cit.),Henrot's[24] and Valat's[25] are others. In Murray's case,a female,37,[26] it is to be noted that incomplete osseous union of the phalangeal epiphysis and diaphysis is shown in the skiagrams; this delayed union is now regarded rather as a symptom of hypo-pituitarism. The thyroid disease in acromegaly must be regarded as subsidiary,though as regards associated symptoms and signs it often plays an important,though inconstant,part. In the case of Mrs.B.,we have seen the enlargement was of the nature of a fibrous goître,and the type of goître in acromegaly appears to be the commonest. In the series of Hensdale,of New York,it was found,in 36 cases, 13 times. In our case it was precisely the same (clinically and pathologically) as the many goîtres

examined by us in other people from the same district, where goître was prevalent. Yet, taken in conjunction with the stimulus of frequent pregnancy, it may have had some influence tending to pituitary over-action. We have noted the close functional association of the thyroid with the reproductive organs, and it is remarkable how uniformly these suffer in connection with "anomalies of growth." The influence of the thyroid over growth is well recognised. In pancreatic infantilism, exhibition of pancreas will stimulate the metabolic processes concerned in growth. Probably many internal secretions are concerned, the pituitary being the "growth regulator", or proportion regulator", as suggested by Woods-Hutchinson. With regard to the disturbance of sexual function, we may note that the full acquirement of the sexual powers seems to stand in relation to cessation of growth in the normal individual. In some individuals great increase in stature, without acromegaly, has been found along with imperfect development of the reproductive apparatus, e.g., Thompson's quoted case.(27) It is frequently noted amongst domestic animals that castration when they are young tends to produce large size. Eunuchoid giantism has received attention from Vidal and Picqué(28) and others, who have demonstrated the

connection between the genital apparatus and the growth of the skeleton and shown that the hypophysis cerebri is not exclusively concerned in excessive osteogenesis. In this connection,Keith's theory,which has been considered,will be remembered. With regard to giantism in general,the earlier views that acromegaly is nothing else than "late giant growth"(Massalongo) and that "gigantism is acromegaly in youth"(Brissaud and Meige) have now more support than the view of Sternberg that "giant growth predisposes to the appearance of universal dystrophies,and especially of acromegaly." About 14% of cases of acromegaly begin before 20 years of age,and Sternberg states that gigantism occurs in 20% of the cases. Langer found hypophyseal enlargement in all the giants he studied,according to Klebs. Sternberg,however, stated in his monograph that this was a false citation by Klebs of Langer's results. A small proportion of giants have been "normal giants,"according to Sternberg,that is to say,though of unusually great stature,they have shown no marked deviation in form or capabilities. The greatest number show acromegalian features and have,in common with acromegaly,pituitary affection.

After considering the matter in 1902 in connection with the case of Mrs.B.,we noted that,"it appears that,though the two processes may not be identical,yet the etiological factors are in close

relation,and if operating in youth,without special inhibitory complications (e.g.,thyroid defects),have largeness of body as well as acromegalian features as a result,something depending on the period of incidence." After studying the work of Keith and others,we are the more confirmed in the idea of the identity of the processes.

Course: Prognosis: Treatment.

Some cases run a rather rapid course. Those belonging to the acute group of acromegaly, of which Sternberg found 6 examples out of 125 cases, have a course of three or four years. Others last a dozen or fifteen years, and some have lived to a normal age. Acroparaesthesia, pains in the limbs and weakness, and cessation of menstruation are experienced in many cases early in the disease. Headache, too, is often an early symptom, and is usually one that persists throughout, though there may be intermissions. Very frequently visual disturbance, e.g., the "blinker sensation" is what brings the patient to the doctor. The acroparaesthesiae seem to accompany the establishment of the changes and pass off afterwards. Galactorrhoea, often arising along with the cessation of menses, may persist for some years. Its presence was noted in Mrs. B's. case. Occasionally urgent cerebral symptoms are rapidly developed, which have been known to pass off leaving marked visual defects. Cachexia in the acute cases, with stuporose condition, may be so pronounced as to demand operative relief, though the general condition may permit of only an operation designed to lessen pressure in the cranium. Even considerable visual disturbance may abate considerably of itself. The re-

establishment of the menses is a good sign, especially in cases where cachexia is not marked and where eye changes are not pronounced. Remission of headaches is a hopeful indication. Violent headaches, when persisting, constitute an indication for operation. A patient whose symptoms have been in evidence for a long time, may, caeteris paribus, be given a more hopeful prognosis as regards duration of life than an early case where the future course is more speculative. Glycosuria, polyuria with polydipsia, and bulæmia may all pass off. In the chronic cases, ability to work may return. This occurred in our case; also in cases reported by Sternberg and by Denti, Schlesinger, and Kojewnikoff (Sternberg). Such remissions may amount to a year or more. Abatement was noticed by Marie in his original two cases, in the first one for a period of three years.

Klebs considered the dilatation of vessels as primary("active phase"), while Sternberg thought it more likely to be secondary to atrophy of "muscular and elastic constituents" and fibrous tissue replacement. To take the vascular sclerosis to follow the increased vascular activity(associated with the growth changes) is in more accord with the phases of vascular change occurring in the life-history of the normal individual. The frequency of indications of vaso-motor disturbance in the early stages supports Kleb's view. The fact that the sclerosis may be widespread and affecting all symptoms, including the vascular, may be adduced to

support Sternberg's suggestion. The enormous increase in the size of the temporal muscle (discussed by Keith) has been cited as an outstanding example of compensatory hypertrophy to meet the great augmentation in size and weight of the lower jaw (Gibson).[29] The effects of partial thyroidectomy in cases of acromegaly with goître are not uniform. In the case observed by Sternberg in Alibert's clinic, the operation was performed in the early stage of paraesthesiae. Some three months later, the hands, nose and tongue were enlarged: progeneum, exophthalmos and amenorrhoea were established. The result therefore would not appear to be in the direction of arresting the changes.

We have mentioned the subsequent changes in our case, and as they are of a nature to be associated with the rôle of the thyroid, are inclined to attribute them, or their degree and rate of progress, to disturbance of thyroid influence, though such events, it is true, have marked the advance of uncomplicated acromegaly.

Death may occur in the chronic cases from concurrent complications, or from any of the causes of death in prolonged wasting disease. In acute cases, profound toxaemia with cerebral symptoms may usher in the end. Sudden death, as is observed in tumours of the brain, may somewhat unexpectedly occur. In the chronic cases without the complaint of unbearable symptoms, treatment must be symptomatic.

Organotherapy has so far not yielded encouraging results. Thyroid and pituitary administration have in many cases produced rapid loss of weight and increased weakness, and should be stopped at once if a tendency to these is manifest. It would seem that pituitary administration is less likely to be ~~pain~~ harm-ful than thyroid gland. Atropin may be tried if perspiration is very troublesome. Coal-tar derivatives, such as phenacetin, phenazone, etc., often procure relief for the headache.

All measures tending to promote good general nutrition must be adopted. Climato-therapy, especially a change to higher altitudes, may, if possible, be tried. Baths, electricity and massage may provide relief, especially for the painful sensations about the limbs.

With regard to the conditions calling for surgical interference, which is becoming more and more employed, we may note that according to the present state of knowledge it is indicated in the following:- (30)

(i) In all acute cases of acromegaly. The number of successful operations is now considerable, and according to some authorities the condition is never malignant: in any case it is rarely so.

(ii) In profound eye changes occurring in the chronic form. Here Cushing's intermusculo-temporal method of decompression (31) is indicated,

to avert the onset of blindness.

(iii)In the case where the disease has reached the cachectic stage,a decompression operation would be the correct procedure.

With regard to operative measures on the pituitary gland,there are four chief methods which can be adopted:-

i.Temporal.

ii.Frontal(Cushing).

iii.Superior
iv.Inferior } Nasal

i.Cushing states that the temporal route probably will remain for those cases in which a benign tumour or cyst projecting into the infundibular region can be brought into view and attacked from the side. This means that it should project upwards markedly. This method is not now adopted,or only rarely.

ii.Cushing[32] used an omega shaped incision in the forehead,with the base at the root of the nose. He opened the frontal sinus,then the ethmoidal, and so approached the sphenoidal sinus and the sella turcica. Of course a strong,concentrated light is necessary.

iii.Von Eiselberg's method[33] and technique are as follows:- Prophylactic use of urotropine, anaesthesia,packing of nasal cavities,

temporary resection of nose and deflection to the right side, whereby vomer is cut as far back as possible, temporary resection of frontal sinus, total removal of contents of nasal fossa, including posterior part of vomer, exposure of anterior wall of sphenoidal sinus, opening of same and laying bare the base of hypophysis prominence.

iv. Kanavel's method (34). The infranasal route to pituitary "consists in elevating the nose, cutting the cartilaginous septum, removing the middle turbinates, deflecting the bony septum, locating the sphenoidal foramina, cutting off the intervening attachment of the perpendicular plate of ethmoid and vomer, entering sphenoidal cells, and thus reaching the floor of the sella turcica."

Conclusions.

As regards the operation, it has been proved that an acromegalous patient can stand loss of blood, can bear a somewhat severe operation, and exhibit even less reaction than is ordinarily met with in such operations, and show a healing power fully up to the average.

The skeletal changes in acromegaly are the most definitely characteristic of the disease, and great attention must be paid to these in making a differential diagnosis. The osseous changes are of the nature of normal growth, with, however, a disturbed proportion between the normally correlated processes of bone formation and bone absorption. It is feasible that a hormone acting upon osteoblasts is concerned in rendering them responsive to the mechanical stimuli to which they are subjected, and that in acromegaly the osteoblasts are rendered unduly sensitive. This hormone is the product of the anterior part of the pituitary gland, which, if acting excessively, will produce giantism if influencing the immature skeleton, and will produce acromegaly if influencing the skeleton after full growth is attained.

Though a tumour has usually been found associated with the hyper-secretion, the latter may be manifested in the absence of permanent pituitary structural change, and probably [redacted] routine post-mortem examination of the pituitary body in such

conditions will strengthen the existing evidence, pathological and clinical. The pituitary body may be stimulated to this hyper-secretion by various influences, amongst which disturbances of the thyroid gland and genitals may be cited. Various internal secretions are apparently necessarily concerned in growth, with the pituitary occupying a controlling position, though it is open to doubt if the pituitary disturbance is the ultimate primary cause of acromegaly and giantism.

The view of the relation of the pituitary hyper-secretion to these conditions receives valuable support from the occurrence of conditions such as ateliosis and adipose genital-dystrophy, which are accepted as showing hypo-secretion. The contrast is the most marked in regard to the state of development of the individual, particularly as regards the skeletal structures. It is to be noted also that there frequently occur in the same individual symptoms which are overlapping between hyper-pituitarism and hypo-pituitarism, indicating a multiplicity of function or a variation in the response of other glands to the disturbance of body chemistry.

Many of the symptoms of acromegaly associated with the typical specific bony changes are such as could be occasioned by alteration in function of other organs than the pituitary body. It may therefore be regarded as a poly-glandular

syndrome.

As the symptoms that render life intolerable, or that threaten death, appear to arise chiefly from derangement of the hypophysis cerebri, it is quite justifiable to undertake surgical measures directed towards that organ. A radiogram of the skull is a useful preliminary, since it determines any enlargement of the pituitary fossa and helps the surgeon to gauge the distance to be traversed before the sella turcica is reached.

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