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ACROMEGALY IN ONE OF UNIOVULAR TWINS

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IN the course of an investigation of twins a pair was discovered one of whom showed features of acromegaly while the other did not. They proved to be uniovular twins, and since they now differed so remarkably in stature and general configuration they were regarded as offering valuable and exceptionally rare material for the study of whatever hereditary factors may be concerned in acromegaly.

The twins, Frank and Albert W., are now 46 years old. Their personal histories will be given separately after a brief account of the family history.

Family History.—The family includes Scottish, English and Welsh members; on the mother's side there are many instances of unusually tall stature, none on the father's side.

The paternal grandfather was about 5 ft. 2 in. in height; the paternal grandmother died when the father of the twins was a baby and there is no relevant information about her. The two paternal aunts were both 'little mites' and the only paternal uncle was short and fat. The father of the twins was himself only 5 ft. 2 in. in height. He worked as a fish porter and was healthy for the greater part of his life; he died of a stroke at 65.

The maternal grandfather was a tall man, 6 ft. 1 or 2 in., of Scottish birth, and had two sisters who were tall and 'rawboned.' He was a healthy man, worked as a plumber and gas-fitter and died at the age of 50 through falling off a ladder. Concerning the maternal grandmother no information is available. The mother of the twins is now aged 79 and is still strong, energetic and in good health. She is a big woman, 5 ft. 10½ in. in height; there is no disproportion of features or skeleton. All her sisters are over 5 ft. 8 in. tall, and one of them has married into another tall family, the members of which together with the offspring of the union are shown in the appended pedigree (fig. 3). Her only brother was 6 ft. tall.

The members of the sibship in which the twins occurred are :—

1. Boy who died of fits when four months old.

2. George, age 54. Height, 5 ft. 7½ in. Has seven children, two of whom are similar twins ; none of his children is particularly tall.
3. Robert, age 52. Height, 5 ft. 7 in. Has two sons, of medium height, ages 19 and 17 years.
4. Harriet, age 50, rather short.
5. Emmeline, age 47, average height, married, healthy. Has four children of average height.
6. Frank } twins (see detailed accounts below).
Albert }
7. Caroline, age 41. Height 5 ft. 2 in. Has five children of average height.

FIG. 1.—The twins at the age of 15.

8. Thomas, age 38. Height 5 ft. 5 in. No children.
9. Sidney, age 36. Height 6 ft. 2½ in. Has large hands and features (prominent jaw, long face, size 12 shoes).

Personal History of Albert W.—He was born nine minutes before his twin and was slightly longer and heavier. The delivery, like the pregnancy, was normal. There was only one afterbirth. It is not known whether instruments were used. He had a healthy childhood, except for measles and occasional bilious attacks. Like his twin he did well at school : they got the same marks and did well or badly in the same subjects. At the age of 18 Albert had grown into a very strong youth and became a grave-digger. After five years he was made foreman and has now for many years been general foreman of the graveyard, where he is still capable of exceptionally heavy manual work. His height has certainly not altered since the age of 27, but

in the opinion of his twin brother his face has grown longer in the last few years. There has, however, been no change in the size of his feet or hands or the circumference of his head for the last 20 years. At the age of 21 he ceased to need bigger shoes than the last pair he had worn ; he has had to have his shoes specially made (size 14). He thinks his head has altered in shape the last 10 years.

At the age of 17 or 18 he had trouble with his jaw locking. By the time he was 20 he had such a defective bite that he could not eat nuts or munch an apple ; at 23

FIG. 2.—The twins at the present time.

a dentist found great difficulty in fixing a denture and called attention to the defective development of his temporal muscles, for which he has since received treatment.

He married 23 years ago and has two daughters, ages 21 and 19, who are healthy and not above the average height. He has noticed no lessening of sexual desire in himself, and is potent.

His medical history has been rather uneventful. At the age of 12 he was swinging round a horizontal bar, 6 ft. high ; his hands gave way at the height of the swing and he fell on the concrete floor, hitting the back of his head. It bled a lot but he was not stunned ; he got up straightaway and went home but felt shaky. He returned to school that afternoon but stayed away for the next three or four days. He did

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FIG. 3.—Arrows indicate the twins.

not bleed from the nose or ear, and there were no ocular symptoms or headache subsequently.

Eight years ago he had an abscess in his axilla following a pustule on his finger, and was ill with it for seven months. For six years he has had acne rosacea, attributed by his doctor to digestive disturbances. He is not subject to headaches. He has always been very strong and boxed a good deal in his teens. He is an energetic, rather naive, good-natured man, proud of his height, strength and good health.

Personal History of Frank W.—His birth was normal, his childhood healthy, except for measles and occasional bilious attacks. He married at the age of 23, within two months of the date of his twin's marriage. He has four sons, the eldest of whom, age 21, is nearly 6 ft. tall. His health has been good; he was wounded in the wrist during the War. He is moderate in smoking and in drinking alcohol, but has a very big appetite. For many years he has run a window-cleaning business of his own. He is active, rather impatient, amiable and less naive than his brother Albert.

Points of Likeness and Disparity (as shown in history).—They were very alike during childhood. When they were in bed together their mother would have to turn them over to find a particular scar on Frank's head by which to identify him. They were continually being confused at school, and were usually distinguished by differences in their clothing, such as the number of buttons on the waistcoat. At the age of about 12 Albert's feet were larger than Frank's, but otherwise they took the same size clothing until the age of 14. At the age of 15 they were still so alike that one of them would pass for the other during a conversation of an hour or so with people who knew him well: Albert was, however, by this time, taller than Frank (fig. 1). He then shot up and by the age of 18½ was a very big fellow and continued growing, whereas Frank stopped growing at 17. Apart from accidents, they had during their earlier years the same illnesses and at the same time. Though not strikingly similar in personality, they have always got on very well together and tend to behave similarly in similar circumstances.

Physical Characteristics.—The difference in general appearance is striking. Albert is a giant, with a long face, narrow forehead, prominent superciliary ridges, very deep suprazygomatic hollows, wide-set broad cheekbones, thick lips, very large nose and chin, big hands and feet, thick fingers. Frank's stature and facial configuration can perhaps best be described as ordinary (fig. 2). Albert's bite is defective, the lower jaw being 1 in. in front of the upper when his mouth is closed. His palate is narrow and has a high arch. These features are not found in Frank.

The following measurements were made:—

	ALBERT	FRANK
Anteroposterior diameter of head ...	20.9 cm.	19.3 cm.
Lateral diameter of head ...	14.8 cm.	14.2 cm.
Circumference of head 1 in. above bridge of nose ...	60.0 cm.	55.0 cm.
Chin to hair margin ...	22.4 cm.	19.3 cm.
Nose length ...	7.5 cm.	6.0 cm.
Nose breadth ...	5.4 cm.	3.6 cm.
Ear length ...	7.6 cm.	7.1 cm.
Transzygomatic ...	14.05 cm.	12.8 cm.
Length of upper arm ...	37.7 cm.	34.0 cm.
Length of forearm ...	29.2 cm.	26.5 cm.
Total length of lower extremity ...	94.4 cm.	80.2 cm.
Length of leg ...	46.2 cm.	42.0 cm.
Total height ...	(6 ft. 4½ in.) 194.3 cm.	(5 ft. 8 in.) 172.7 cm.
Total weight ...	16 st. 4 lb.	10 st. 7 lb.
Span ...	(84 in.) 213 cm.	

Colour of hair and eyes is the same in both. Albert's hair is thinner than Frank's. Albert takes size 14 in boots, Frank takes size 9.

The skull and hands of the twins have been X-rayed. In Albert there is much enlargement of the bones of the skull, of the typical acromegalic kind, with large air-sinuses and closed sutures; conspicuous prognathism; no definite alteration in the size and shape of the pituitary fossa. Frank's skull shows no abnormal features. In Albert's hands the bones are enlarged, unduly porous, with exostoses on the phalanges. This is not the case with Frank, in whom the appearances are normal.

Finger prints and palm prints supply evidence for uniovularity which may be regarded as conclusive.

DISCUSSION

The questions raised by this rare instance are (1) clinical, viz. the relation of acromegaly to the non-progressive acromegaloid forms; and (2) pathogenic, viz. (a) the constitutional factor in the development of acromegaloid conditions, and (b) the nature of the environmental factors which may provoke the morbid manifestations.

It may be taken for granted that acromegaly, acromegaloid conditions and gigantism are all referable to variations from the normal in the function and commonly also in the demonstrable structure of the anterior part of the pituitary gland. The second question is therefore one of the inherited and environmental causes of such changes in the pituitary.

The relation of acromegaly to gigantism, first discussed by Massalongo, Brissaud and Meige, Sternberg, and Launois and Roy, has become a more general problem of the relation of acromegaly, the progressive disorder, to other anomalies of growth attributable to changes in the function of the anterior lobe of pituitary and either not progressive or not permanent. Cushing¹⁵ described a condition intermediate between acromegaly and gigantism. Ehrmann and Dinkin have given the name 'Acromegaloidism' to 'geringere, dauernde oder vorübergehende Steigerungen der inneren Sekretion des Vorderlappens der Hypophyse,' of which they report 40 cases. They divided it into familial acromegaloid types, in which the condition was permanent, and actual acromegaloidism, a more or less transient but more marked manifestation of symptoms, occurring at any period of life and approximating more closely than the familial type to true acromegaly in its clinical features. Bauer also has referred to these cases where after development has been completed the external signs of acromegaly are present without evidence of definite progressive disease; for this 'acromegaloid constitution' he is uncertain how far constitutional deviation in pituitary functions and how far autochthonous potentialities in the skeleton and other 'Erfolgsorgane' are responsible. Freudenthal gives a more complicated classification. There are now a great number of these cases on record, and it is certain that the patient Albert W. here described exhibits these acromegaloid characteristics rather than the familiar disease acromegaly. His strength, excellent health and retention of libido all point to this (for the sexual life, cf. Biedl). Many of the cases of acromegaly reported appear to have been examples of acromegaloidism or acromegaloid constitution. The difference is not at present one

that could be inferred from microscopical appearances in the pituitary gland of the affected persons : in both, hyperplasia of the anterior lobe, generally as eosinophilic adenoma, is found. Biedl thinks chromophobe cells may be responsible for transient acromegaloid changes, as in pregnancy. There is no reason to suppose that the clinical differences are of any fundamental type. Whereas there are strong grounds (occurrence of acromegaly in children) for questioning whether mere hyperfunction of the anterior pituitary can during the developmental period be held responsible for gigantism and acting during later life for acromegaly, it seems likely that the same disorder of function is responsible for acromegaly and acromegaloidism, the differences being conditioned by the degree and progress of the disorder of function, and perhaps also by the inherited constitution of the person affected.

The part played by inheritance in acromegaly is commonly overlooked, the question as to pathogenesis and ætiology being often disposed of by reference to the pituitary and other endocrine changes : but these have themselves to be accounted for. One might expect inherited factors to be significant here since there is so close an association between acromegaly (of which a fifth of the cases are giants) in one member of the family and tall stature in other members. A number of cases have also been reported of acromegaly occurring in more than one member of a family. The first report was a dubious instance of Fraentzel (1888), then Arnold (1891), Bonardi (1893), Schwoner (1897), and Cyon (1898) published cases ; and in the present century 20 cases have been reported—by Bregmann (1900), Warda (1901), Fraenkel (1901), Schaeffer (1903), Franchini and Giglioli (1908), Cushing (1912, two cases), Allaria (1913), Sicard and Haguenau (1914), Lewa (1914), Oehme (1919), Machwitz (1920), Nobbe (1924), Möller (1924), Davidoff (1926, four cases), Müller (1930), Kienböck (1931). The papers of Banaudi and Strandell are not available to me in the original.

Of these cases, in four the patient's mother had also shown the disorder (Schwoner, Cushing, Allaria, Schaeffer) ; in four the patient's father (Bonardi, Kienböck, Fraenkel, Davidoff) ; in nine a brother or sister (Cyon, Möller, Müller, Oehme, Sicard and Haguenau, Nobbe, Bregmann, Fraenkel, Davidoff) ; in four a son or daughter (Fraentzel, Machwitz, Warda, Franchini and Giglioli) ; and in three a collateral (Lewa, Davidoff). In three instances more than one of the patient's relatives was affected (Oehme, Fraenkel, Nobbe). Unfortunately data permitting accurate diagnosis are often not available concerning the affected relative ; in some cases the diagnosis is disputed (thus Marie considered the daughter of Fraentzel's case to have shown hypertrophic pulmonary osteoarthropathy, not acromegaly), and for the patient himself it is often difficult to be sure. Thus Lewa's two cousins (in whose family there was much consanguinity) showed changes in the soft parts without skeletal changes, but in one of them the diagnosis was supported by the discovery of an eosinophil adenoma of the pituitary gland. In Arnold's case (which was the subject of a stormy controversy between

Friedreich, Marie, Erb and others), as in those of Müller, Oehme, Kienböck, Sicard and Haguenau, Allaria, Warda, Bregmann, and Fraentzel, the changes in the affected relative were circumscribed and anomalous, suggestive of macrosomia; Müller would regard his own case as well as Arnold's and Oehme's as representing a special hereditary disorder. Apart from these somewhat doubtful examples one finds cases where the patient is acromegaloid, e.g. Cushing's kyphotic man, whom he described as intermediate between acromegaly and gigantism, or Nobbe's woman of 40, though the majority of the patients themselves are typical examples of slowly progressive acromegaly. Among the relatives, however, only a few showed definite acromegaly, e.g. the cases of Schwoner, Machwitz, Schaeffer; in many the diagnosis is doubtful since one is dependent on hearsay, photographs, etc.; in other the condition was probably an acromegaloid one (Bonardi, Nobbe, Fraenkel). In four of the families other relatives were unusually tall (Schwoner, Cushing—both cases, and Nobbe). In three cases the pituitary disorder was associated with other endocrine anomaly in the same person (thyroid disorder in Möller's cases, diabetes mellitus in that of Schaeffer and Machwitz). Several instances, like those of Parhon and Cernantzeano, Étienne and Richard, may be found in the literature describing a patient with acromegaly who had a relative with hypopituitary features: a third brother in Cyon's sibship had pronounced symptoms of this kind. Such cases have been omitted from the series here collected, which is concerned only with the occurrence of acromegaly or acromegaloid features in several members of one family.

Reviewing these cases it will be seen that in the relatively large literature of acromegaly very few examples of a familial incidence have been reported (cf. Falta). Among these anomalous forms have predominated; in the same family definite acromegaly of early or late onset, acromegaloid features of a mildly progressive or stationary kind, or partial enlargements of the extremities may be found. It would appear that the hereditary factor is for the most part unimportant in acromegaly but that in some families there is an inherited predisposition to pituitary anomalies in the direction of perverted or overactive function of the anterior part; this predisposition only becomes manifest in certain rare circumstances, and the modes of its manifestation are variable. This agrees with the views of Bauer. The conditions for its manifestation are most commonly satisfied in ordinary tallness hardly amounting to gigantism, most rarely satisfied in severe progressive acromegaly.

In so far as the patients reported in this paper are unquestionably uniovular twins, their hereditary equipment may be assumed to be identical or almost identical. Since one of them, Albert, is an acromegaloid giant and the other not, it may be assumed that environmental conditions have been present which favoured the manifestation in Albert of his predisposition to a pituitary anomaly. That such predisposition was present in both of the twins is probable when one considers the large number of antecedents and collaterals

of unusually tall stature and the fact that the twin of normal height (5 ft. 8 in.) has a son who is 5 ft. 11 in. high at the age of 20.

What then are the environmental factors which have favoured the acromegaloid manifestations in one of these twins? The brothers were almost identical in appearance and size until the age of 14: then Albert began to grow faster and was soon noticeably taller, bigger and stronger than Frank. It may therefore be assumed that any environmental factor responsible for Albert's more rapid growth had been operative before this. The only circumstances that one can regard as significant in this connexion, with one's knowledge of the patients' histories, is the accident which Albert had at the age of 12. The significance of cranial trauma in the ætiology of acromegaly is usually thought to be very slight. Bassoe denies it any. Cushing reports no instance of it, though in six of his cases of hypopituitarism there was a history of cranial trauma; Davidoff reports two cases out of a series of a hundred acromegalics; Bauer says that physical trauma seldom plays a part in the ætiology of any endocrine disorder. There are, however, two striking cases in the literature. Nobbe reports a man who shot himself in the head at the age of 16, causing fracture of the base of the skull, followed by polydipsia, polyuria and loss of libido, and later by rapid and excessive growth of the long bones, with prognathism and enlargement of the nose, lips and tongue. A radiograph taken at the age of 23 showed a bullet in the sella turcica; there were also X-ray evidences of acromegalic changes in the bones. Bleibtreu reports a less striking but still more relevant case. A boy of 16 fell downstairs and hit his head, but the injury was regarded as trivial and he did not have to lie up after it. Next year he was observed to be growing very rapidly and by the age of 21 his height was 196 cm. (6 ft. 5 in.); his superciliary ridges, nose and lips were thick and prominent. At autopsy, following his death from tuberculosis, the sella turcica was found filled with a mass of golden pigmented fibrous material in which pituitary alveoli were seen on microscopical examination. It is not certain that the trifling injury recorded in this early case was responsible for the hæmorrhage into the pituitary with subsequent changes, leading to the appearance of acromegaloid features, but there was no other explanation forthcoming for the lesion found: and if it be accepted, it may be regarded as furnishing support, however slender, for the view that cranial trauma played a similar part in the genesis of Albert W.'s acromegaloid condition.

The final point of interest in this case lies in the object-lesson which it provides that very close similarity of adult twins as to appearance and measurement must not be taken as the only or essential criterion of uniovularity. It might be most misleading, as in this case. (The earlier history, also finger and palm prints, put the uniovularity here beyond dispute.) Minor variations in uniovular twins have been recorded. Weitz has found deviations in body weight and size of skull of uniovular twins but none as great as in this pair. There is no other case of acromegaly in indisputable uniovular

twins on record. Allaria's doubtful case (a child of 21 months) was a twin, but there is no information in the report as to points of likeness or dissimilarity except that one of the twins was healthy and the other had macrodactyly. Möller describes two brothers, twins, who showed ichthyosis shortly after birth and ever since; one of them at 16 began to grow rapidly, especially as to the extremities and nose, and also had pains in the head, dizziness, tiredness and mental retardation. He is now 158.5 cm. high and has large hands and feet, lips and tongue. The other twin has shown marked enlargement of the nose, but no enlargement of the hands and feet, and no headaches, tiredness or retardation. His height is 162 cm. The author regards the condition as a pluriglandular syndrome in which thyroid and pituitary are chiefly concerned. He does not give sufficient information to enable one to decide whether the twins were uniovular; in a photograph they look very alike. Siemens has reported many cases of thyroid disorder in uniovular twins without divergence, but there is an interesting communication by Borchardt showing the influence of exogenous factors working through the endocrine glands. It is, however, a rare conjunction that could result in so dramatic and instructive a divergence between so-called identical twins as that reported here.

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