to peculiarities inherent in the germinal cells of the parents. This view is supported by the observations of Engel-Reimers,[19] who has emphasized the fact that excessive muscular development, the so-called "athletic habitus," appears to be due to an abnormal hereditary predisposition and not to hypertrophy from functional overactivity. This is well borne out by the physical condition in new-born giant children. They frequently present the athletic habit. The head is about the size of that of the normal infant, but the trunk is massive. Now this hypertrophy, if we can call it such, is clearly not due to mechanical work nor to compensation, nor to the other ordinary causes of overgrowth. It must be due to some disturbance of nutrition. The relative importance to be attached to peculiarities of the male and female germ cells is still in doubt, for in the recorded cases we rarely have any statement as to the physical condition and development of the father. From the instances cited it is evident that both germinal elements may play a part. But it is equally evident that some idiosyncrasy in the maternal organism alone is sufficient to produce the result. In Fuchs' case, for instance, the father is noted as having been in a poor state of nutrition. This has led Werth to suggest that the tendency to produce large children is due to an inherent peculiarity of the ovum, possibly to its large size. However this may be, we have sufficient evidence to show that large size on the part of one or both parents is not necessary to produce the result in question. Yet it seems probable that physical superiority in the mother, if not in height, at least in physical constitution and nutrition, is an important etiological factor. In 178 cases of large and giant children collated by Fuchs, 166 mothers are noted as being of more than usually strong physical development and nutrition. The remaining 12 were weakly, but in no case did their children exceed 4.36 kgm. in weight, a size which, according to our adopted standard, cannot be regarded as gigantic. In view of this fact we see that the influence of maternal development and nutrition assumes considerable importance. Exceptions to this, however, occur. In a case cited by Dubois, a woman with extensive tuberculosis gave birth to a child weighing 6.336 kgm., and another with severe diabetes had a child of thirteen and a half pounds. Two possibilities must evidently be considered in this connection, a primary peculiarity of the ovum or sperm cell, or both, and a condition of increased intra-uterine nutrition. The influence of peculiarities of the primitive germinal cells would perhaps be best illustrated by instances of the atavistic manifestation of gigantism, or in those cases, like that of Dubois, in which the maternal organism was conspicuously weak, for in the latter case increased intra-uterine nutrition could obviously play no part. Some of the forms of minor terata, such as polydactylism, are no doubt also of this nature. Polydactylism has been known to run through a family for three, four, or even five generations, being eradicated only in process of time by marriage with normal persons. Curiously enough polydactylism has been found associated both with dwarfism and with gigantism. It has been thought by some that mothers in whom the function of menstruation was established early were more likely to have larger children than others, apparently on the theory that such persons were possessed of greater reproductive energy. Negri on the basis of 333 observations has stated that the children of mothers who began to menstruate early were both larger and heavier than the offspring of those whose menstruation was late in coming on. This has not been confirmed, however, by other observers. The point can probably not be decided until more studies on the subject are forthcoming. It is, nevertheless, true, so far as the records go, that large children are more likely to be borne by those who are at the height of reproductive activity and who have had previous children. In elucidation of this point we may perhaps quote Fuchs' statistics. In 176 of his cases, already referred to, the age was ascertained. These were divided as follows: I. Under twenty years, 5; of this number 5 were primiparæ. II. Twenty to twenty-five years, 72; of this number 18 were primiparæ. III. Twenty-six to thirty-five years, 75; of this number 2 were primiparæ. IV. Thirty-six to forty-eight years, 24; of this number none were primiparæ.

Between the ages of twenty and thirty-five, the years of the greatest sexual activity, the number of large children was greatest. Now, taking the third class, we find that only 2.6 per cent. were primiparæ. If these results be compared with those obtained from a series of 1,000 normal births, in 342 of which the mothers belonged to the third age period, it will be found that there were 57 primiparæ, a proportion of 16.9 per cent. This corroborates the observation made a little while ago that certain women show a tendency to produce large children, or in other words that the tendency once manifested tends to perpetuate itself.

Intra-uterine nutrition is undoubtedly a factor of considerable importance. In the article on *Dwarfism* or *Nanosomia* in this volume the rôle played by intra-uterine malnutrition in the causation of inhibited growth is dealt with at some length. Here syphilis, alcoholism, and tuberculosis, together with lesions resulting in interference with the free circulation of blood through the placenta, are of importance. Conversely, an overplus of nutritive energy might be expected to produce its effect upon the fruit. In this connection we have to take into account the condition and surroundings of the mother during pregnancy. Pinard (cited by Bouchacourt[20]) compared the average weight of 500 new-born children whose mothers had worked up to the time of delivery with that of the same number of children whose mothers had rested during the later weeks of pregnancy. He found a notable superiority in weight and nourishment in the offspring of the latter class. In a similar inquiry Bachimont (cited by Bouchacourt) in a series of 4,445 observations found the excess in weight for the latter class of children to be, on the average, 300 gm. In this particular it should be remarked that very large children lead perforce to a condition of complete inactivity and inertia on the part of the women pregnant with them. This of course means rest which tends to increase in turn the size of the child. Thus a vicious circle is induced. The importance of intra-uterine nutrition in modifying the weight of the fruit is well illustrated by the good effect of dieting in those cases in which a woman has either a tendency to produce large children or else has some contraction of the pelvis. By this procedure it has been found possible to deliver such a mother of a living child.

Some attention had been directed to the subject of prolonged gestation and its effect in producing large children. The statistics seem to show that this factor has a certain amount of importance, but it is probably effective only when combined with other causes. It does not seem to me, however, that it is justifiable to place cases of this kind in the same category with giant growth. If, for example, a child is retained within the uterus for three hundred and eight days instead of two hundred and eighty, it is practically in the same position as an infant one month old, due allowance being made for differences between intra-uterine and extra-uterine modes of nourishment. Such a child would derive no permanent advantage from its prolonged retention within the uterus, and would probably develop later much as other children do. In other words, the vitium of excessive growth is not inherent. Unfortunately many of these points we have touched upon cannot be verified by any large series of observations. Gigantism in the first place is much rarer than dwarfism. Then the majority of giant children are still-born. Even those cases in which giant growth manifests itself later in life are beset with difficulties. The number of carefully made studies is not great and prolonged observation is rarely possible, not only from the fact that giants are apt to die early, but on account of their nomadic kind of life.

In dealing with the question of heredity we have adduced numerous facts to show its importance in the causation of anomalous forms of growth. The influence of

this factor, while perhaps more direct and striking in the case of giant births, is nevertheless, as we have shown, to be taken into account in the post-natal forms. But besides this we have to consider the bearing of internal metabolism on the subject. The more recent work done on cretinism and the results of the experimental removal of the thyroid gland have taught us that a condition of athyroidea, which undoubtedly acts by perverting the metabolic processes of the organism involved, has a profound effect on the function of growth and development, namely, in the direction of inhibition. In that other most remarkable perversion of growth, acromegaly, where there are enlargement and deformity of the body, or excessive growth, gross lesions of the pituitary body have been found. Disorders of internal secretion obviously are of some importance.

The general resemblance between acromegaly and gigantism has led to the promulgation of the view that the two conditions are one and the same thing, and the controversy over this point has waxed hot and heavy. Without being prejudiced on either side, I think that the careful observer cannot fail to be impressed with the parallelism which exists between the two affections. Brissaud and Meige have been the chief exponents of the identity theory, while Marie, who first differentiated acromegaly as a disease entity, though he has somewhat receded from his first position that acromegaly and gigantism are entirely distinct, has not been entirely convinced by the arguments adduced against his position.

Marie in his first studies on acromegaly summarized it as a peculiar affection, characterized by a massive hypertrophy of the bones of the extremities and the extremities of the bones. He admitted that a number of cases had been confounded with gigantism, for the reason that attention had been directed to the excessive height to the exclusion of the less obtrusive signs, while the disease in those of normal stature had been overlooked. Shortly after, Guinon,[22] following Marie's lead, took the same position that the two affections were essentially different, on the ground that as our knowledge had increased it had to be recognized that persons with acromegaly were by no means always gigantic; in fact they were often below the average height, and again that the configuration of the body was different in both. The various parts of the face and limbs preserved their normal proportions in gigantism while the course of the two affections was different. Guinon even went so far as to state that gigantism is as a rule simply an exaggeration of a normal process, while acromegaly is a disease. It is undoubtedly a fact that typical, or what we might call "text-book" cases of the two affections present an entirely different picture. There have been some giants that presented none of the morphological characteristics of acromegaly, as there have been persons with acromegaly that were not giants. It ought to be unnecessary, however, to point out that even the best-known diseases present at times wide variations from the type. The case of typhoid fever, for instance, need only be mentioned. This being the case it by no means follows that two diseases, at first sight dissimilar, have nothing in common, or even that they are not due to the same cause. The point may be further illustrated by the history of cretinism and myxœdema. At one time it was believed that these conditions, which in many ways are so unlike one another, at least to superficial examination, were distinct diseases. More careful study has, however, shown that both depend on a condition of athyroidea, and few will be found now to deny that cretinism and myxœdema are one and the same thing. The modifying factor has been found to be the age and the concomitant stage of development of the affected individual. If athyroidea becomes manifest in infancy before the bony skeleton is consolidated we get cretinism. If it develop later, when the bony skeleton is complete, the soft parts only are involved and we get myxœdema. It is unsafe then to conclude that one and the same cause may not at times produce widely different results. In other words, the trophogenic function of the individual may be so predominant that it is sufficient to alter a morbid state almost beyond recognition. It has already been pointed out that the normal process of growth manifests itself most strongly at the epiphyseal ends of the long bones, and that increase in length of the bones is possible only so long as the epiphyseal discs remain ununited, save by the softer structures, to the diaphyses. Similarly, the abnormal processes of growth, such as dwarfism and gigantism, manifest themselves at the same points. Deficient vegetative energy in early life will result in stunting the growth of the long bones, and the same thing will happen if the epiphyseal cartilages are prematurely ossified. Excessive vegetative power during adolescence results in increase in height; if synostosis of the epiphyses has taken place, as occurs in adult life, then it is conceivable that, increase in length being impossible, increase in breadth and thickness must occur. Do, then, acromegaly and gigantism bear to one another a relationship similar to that existing between myxœdema and cretinism? Many facts point in this direction. Numerous observations have shown that acromegaly frequently supervenes in gigantism. Surmont[23] in 1890 reported a case of acromegaly in a girl of eighteen, in whom the symptoms were preceded by a notable increase in the size of the body. The enlargement was generalized, but most marked at the extremities. Byrom Bramwell[24] mentions the case of a giantess who was attacked by acromegaly. Swanzy[26] also demonstrated the lesions of acromegaly on the skeleton of McGrath, the Irish giant, before the Royal Academy of Medicine of Ireland. Shattock[27] believed the skull of O'Brien to be acromegalic. In 1893 Dana[16] published two cases of acromegaly associated with gigantism, and he remarks that the coincidence of the two affections is more common than has usually been supposed. He further mentions a great many symptoms which they have in common, and brings out the most important point, viz., that out of twelve autopsies on giants the pituitary body was enlarged in ten. In the case of "Adma," a French giantess, who died at the age of twenty-one, measuring six feet eight and a half inches, Hutchinson states[28] that the face and extremities presented the well-known features of acromegaly. At the autopsy the pituitary gland was found to be considerably enlarged. A striking case, also, is reported by Brissaud and Meige.[21] J. P. Mazas, the giant of Montastruc, began to grow rapidly when thirteen years of age, and became very strong and robust. At twenty-one years he was 212 cm. high, eventually reaching 220 cm. At the age of thirty-seven he experienced a severe pain in the back, which he attributed to lifting a heavy weight. Deformity of the back set in and his height began to diminish. He gradually developed enlargement of the face and extremities, headache, weakness, intellectual and sexual torpor, and all the classic symptoms of acromegaly. Sternberg,[29] also, in an elaborate paper on the subject found signs of acromegaly in forty-two per cent. of giants. More recently Walker[30] reported an instance of acromegaly in a boy, who began to grow rapidly when six years old, and who at sixteen was six feet five and a third inches high, and weighed two hundred and forty-five pounds. Bonardi[15] refers to the case, already mentioned in another connection, of a boy who at the age of fifteen had the size and development of an adult male. When twenty-two years old he began to suffer from pains in the head and nausea. Soon after, general weakness set in, with enlargement of the hands, feet, maxillæ, and tongue. At twenty-nine he was 194 cm. high and was typically acromegalic. By a careful study of the recorded cases we see, therefore, that a considerable degree of parallelism exists between the two affections. Perhaps the most important points are to be noted in the skeleton.

The typical features in acromegaly are enlargement of the bones of the face and extremities. The hands are "spade-like," and the fingers rounded. In severer cases all the bones of the body become involved. The thorax enlarges and the trunk becomes scoliotic, so that a loss of

height takes place. There exist, however, lesser disturbances of bone formation that are difficult to class, being on the border line between gigantism and acromegaly. In such cases the dystrophic disturbance is confined to one or more parts of a member, or to two members symmetrically. Such malformations may be both congenital and acquired. Of such a nature are those cases in which there is deformity of the face without enlargement of the hands. Chauffard[31] reports a case in which a man of thirty-two presented the features of prognathism, macroglossia, prominence of the external occipital protuberance, headache, anæmia, loss of vision to the right, and slight kyphosis. Some of the anomalies, then, that are to be found in acromegaly may be found without the other features of the disease in certain forms of developmental dystrophy, and may arouse a suspicion as to the acromegalic nature of the case. When such peculiarities are met with in giants we may properly inquire whether they are the stigmata of acromegaly, or whether they merely simulate that disease. In giants thickenings of the extremities of the long bones, hyperostoses, and exostoses have been noted, identical with those that for so long have been regarded as characteristic of acromegaly. Deformities of the knees, which as Osborne, Middleton, Schultze, Hitschmann, and Roswell Park have shown, are fairly common in acromegaly, have also been met with in gigantism. Lucas Championnière in 1899 demonstrated to the Academy of Medicine a giant, aged twenty-seven, who measured 203 cm., and presented an extreme genu valgum. This peculiarity has a double interest in that it affords a link between acromegaly and gigantism, and also connects the latter with infantilism. The curvature of the spine and the rounded thorax, so often found in acromegaly, have been found in gigantism, but our information is defective in this regard.

With respect to muscular power great variations may occur both in gigantism and in acromegaly. Several observers, notably Meige, Dallemagne, Virchow, P. Marie, Souza-Leite, Bourneville, and Regnault, have noted acromegaly developing in persons of exceptional muscular vigor. Some giants, like the Emperor Maximin and the Countess Lodoïska, have been of great strength. This, however, seems to be the exception. Geoffroy Saint-Hilaire states that giants are "without activity, without energy, slow in their movements, avoiding work, quickly fatigued; in a word, feeble in body as well as in mind." Amyasthenia and general weakness are by no means uncommon in acromegaly.

As is well recognized there is a characteristic facies in acromegaly. Meige is our authority for the statement that giants who are still in the period of growth present no special facial peculiarities. In those who have ceased to grow there is an exaggerated development of the face as compared with the cranium. We can sometimes note that the malar eminences are prominent, the lower jaw enlarged, and the angle widened, while the lips are thick. The beard is often thin, the skin thick and dark, the pupils dull, and the whole appearance lacks vivacity. These peculiarities are by no means invariable in giants, nor indeed are they so in acromegaly. We have to allow here as elsewhere for individual variations. In fact, we may perhaps with Hoffmann distinguish between acromegaly of the soft parts and acromegaly of the bones.[32] Meige is, on the whole, inclined to believe that the face in giants at one time approaches the acromegalic type, at another the infantile.

Vascular disturbances have been found in both acromegaly and gigantism. In both the pulse is slow, the circulation sluggish, and there may be varices.

Pains in the head have been found in both affections. Pains also in the limbs, vertebral column, and the viscera, have been met with in about half the recorded cases of acromegaly. These may simply amount to a sense of fatigue or lameness, but may be actually articular, muscular, or neuralgic. It is a popular belief that rapid growth in children is associated with "growing pains," and it is interesting that the same thing has often been noted in giants. In the case of McGrath, for instance the increase in growth was associated with the most violent pains in the limbs.

Visual disorders have been met with both in acromegaly and in gigantism. In acromegaly, at least, they have been found to be dependent on the presence of a tumor of the pituitary body.

Polydipsia, polyphagia, and abundant sweating have been observed in both affections. Polyuria and glycosuria are occasionally met with in acromegaly and in giants who become acromegalic.

In both gigantism and acromegaly there is often to be noted sexual frigidity in the male, and amenorrhœa in the female.

To sum up, the two affections frequently have the following symptoms in common: asthenia in the widest sense of the term; muscular weakness, notwithstanding the absence of atrophy; intellectual degradation; melancholy; headache; diminution of sexual desire in the male; amenorrhœa in the female; alterations in the skin; varices. Lastly, of a great importance, lesions of the pituitary gland have been found in a majority of both affections.

Further, the influence of heredity is marked in acromegaly as in gigantism, and indeed it is not uncommon in probing into the family history to find that acromegaly and gigantism are liable to be met with in the same family. Schwoner, for instance, records[33] a case of acromegaly in a woman of forty-five, whose mother had become acromegalic at fifty. All the members of the family on both sides of the house are noted as having been of great stature. Lackey[34] describes a case of acromegaly in a negro who reached the extraordinary height of eight feet six. His grandfather is said to have been a giant.

In view of the facts outlined above, Brissaud and Meige would discover a general principle underlying the dystrophic disturbances that result in excess. Growth at all periods of life tends to be manifested most conspicuously at the epiphyseal ends of the long bones. The effect produced is controlled by the age of the patient, or, in other words, by his vegetative capacity and the condition of his epiphyseal cartilages. The same pathological process which in the young gives rise to gigantism will, if continued after the normal period of growth in stature is passed, cause acromegaly. If it becomes operative in later youth, when the bones are largely formed but growth is not complete, we get a combination of acromegaly with gigantism. This is to some extent corroborated by the lesions in acromegaly, for, as Marie himself has shown, in cases of acromegaly that begin early in life, the extremities are more elongated than thickened, and are quite unlike the spade-like extremities characteristic of the disease as it occurs in later life. Further, it may be safely stated that acromegaly has never preceded gigantism, while acromegaly has succeeded gigantism in almost half the cases. Brissaud and Meige, however, would go further. They see the same principle at work in the chronic rheumatism so-called of the aged, in rheumatoid arthritis and gout; in youth, in gigantism; in adult life, in acromegaly; in old age, in nodes. They support this by an observation made by Gaston and Brouardel[35] with the *x*-rays on a woman of sixty, who began to show signs of acromegaly at forty-two after the menopause. The disease was slowly progressive, and thickenings in the form of nodules could be made out on the epiphyseal lines.

Without endorsing the rather startling proposition put forth by Brissaud and Meige, that "acromegaly is gigantism of the adult; gigantism is acromegaly of adolescence," it seems to me that the unprejudiced observer cannot fairly deny that they have proved their main contention. There is undoubtedly a close connection between acromegaly and gigantism, and the two affections in a large proportion of cases merge gradually one into the other. Gigantism frequently becomes acromegaly. But how about the other fifty-eight per cent. of cases of gigantism that present no signs of acromegaly? Are these, too, of the same nature, or are they in a different category? It is not impossible nor even unlikely that

some of them are due to the same factors as acromegaly, as it is ordinarily understood. Here we have to consider the natural variations of disease. Diseases do not invariably run their course. They may become ameliorated or may be aborted. Acromegaly itself may present an extremely slow progression, and in fact may cease to advance. A fatal termination does not always occur. It may well be, therefore, that acromegaly beginning in early adolescence may progress only sufficiently far to produce increase in length of bone without the other signs supervening. It may be recalled in this connection that the majority of giants die early. Byrne, the Irish giant, died at twenty-two; James Toller at twenty-four; the "Queen of the Amazons" at about twenty. This may perhaps be the effect of the acuteness of their malady, but in many cases it is due to intercurrent disease, as the resisting power of giants is notoriously low. However this may be, it is plain that many giants die before the period of age incidence of acromegaly, that is to say, before adolescence is completed. We cannot therefore say that they would not have become acromegalic had they lived. It is possible, therefore, that the majority of the cases of gigantism are dependent on the same pathological factors as acromegaly.

There has been considerable debate as to the exact nature of the cause or causes at work in acromegaly. Klebs advanced the theory that acromegaly is due to angiomatosis. Vascular lesions are undoubtedly present both in acromegaly and in gigantism. Witness the arteriosclerosis, the varices, the vaso-motor ataxia, and the hypertrophy of vessels to adjust themselves to the increased size of the body. But there is no proof of any new formation of vessels. Lancereaux, again, has suggested that it is a trophoneurosis. The enlargement of the hands and the disturbed innervation met with in syringomyelia might suggest this. This view is not, however, supported by any known facts. von Strümpell has thought that it is a congenital dystrophy. The majority of observers are, I think, practically agreed that acromegaly is dependent on some gross lesion of the pituitary body, in the form of hypertrophy, cystic growth, adenoma, or other tumor growth. Osborne believes that gigantism in its perfect development is due to a normal hypertrophy of the pituitary gland; that is, to a hypersecretion occurring at the age of puberty or age of general or symmetrical body growth and development. He believes further that gigantism will remain such as long as the pituitary body is in normal hypertrophy, but that these cases of gigantism will assume later an acromegalic type, if, as is often the case, the pituitary body begins to take on pathological conditions. In other words, he believes that an excess of normal secretion from the pituitary gland is the cause of gigantism, while perverted secretion is the cause of acromegaly. This conception is very different from that of Brissaud and Meige, in that it attributes the lesions, which we call gigantism and acromegaly, to two distinct and separate states of the pituitary function. Brissaud and Meige's view implies that the same condition of the pituitary function is at work in both cases, any differences in the results produced being attributable to the age period at which the process begins. We know so little of the nature of the normal function of the pituitary body, and indeed of its disturbances, that it would be hazardous as yet to express an opinion either way. For my part I cannot understand the term "normal hypertrophy," as applied to the pituitary. We have, it is true, what might be called normal or physiological hypertrophy in the case of the pregnant uterus and possibly in the functioning breast, yet this is but a temporary condition and is paralled, so far as I know, nowhere else in the body. Gigantism is an abnormal condition, and to my mind cannot be explained on the basis of a "normal" hypertrophy. It may, however, be true that it is due to an excess of pituitary secretion. But if this can produce increase in the length of bone, why is it not also competent to produce increase in thickness of bone? One seems as likely as the other. Whether acromegaly is due to a hypersecretion on the part of the pituitary, as many seem to think, or to a diminution of the secretion, or again to a perverted secretion, cannot, however, be regarded as settled. Tumors, cysts, and plain hypertrophy of the pituitary have been found in the majority of autopsies on acromegalic cases, and tumors of the pituitary in acromegalic giants (Buday u. Jancto,[36] Oestreich u. Slawyk[37]). Possibly simple hypertrophy or adenomatous growths may imply oversecretion; but cysts or destructive tumors, like the sarcomata that are so frequently found, might be interpreted as lessening the amount of secretion. Conversely, tumors of the pituitary may exist without signs of acromegaly, as in two cases that have come under my own observation. Both were malignant (one sarcoma and one endothelioma). Here we must assume either that the pituitary was able to furnish the proper amount and kind of secretion, or else that compensation had taken place. We are realizing more and more the importance of the principle of compensation in regard to the body metabolism. We see, for instance, that there is a close relationship between the thyroid gland and the pituitary body. In acromegaly the thyroid gland has been found hypertrophied, cystic, or atrophic, and the disease may be complicated by the symptoms of exophthalmic goitre or myxœdema. In this connection may be mentioned a most remarkable case, reported by Pope and Clarke,[38] in which a man suffering from acromegaly had a daughter with myxœdema and an atrophied thyroid, who at the age of twenty presented the physical and mental characters of a child of five. Ponfick, Hymanson, Pineles, and Green, in particular, have noted the association of acromegaly with myxœdema, and Murray[39] its combination with exophthalmic goitre. Conversely, the pituitary has been found enlarged in cases in which the thyroid was atrophied (Boyce and Beadles[40]), and when this occurs it seems to prevent at least the immediate results of thyroid defect, namely, cretinism or myxœdema. In the article on *Dwarfism*, by the present writer, in this volume, the relationship of thyroid dystrophy to that other anomaly of growth allied to gigantism, namely, dwarfism, is dealt with at length, and it is there shown how the condition of athyroïdea may result in inhibited growth and genital insufficiency. The stigmata of infantilism in acromegaly and in gigantism have suggested the possibility of disorder of the thyroid in these affections, and there have not been wanting those who would attribute acromegaly to thyroid dystrophy. Facts, however, do not favor this view.

Genital hypoplasia and malformation, as well as genital inadequacy, have been met with in dwarfism, cretinism, infantilism, gigantism, and acromegaly, and this leads us to discuss in how far disorders of the sexual apparatus are responsible for anomalies of growth. In this connection a number of interesting facts may be adduced. The sexual languor, as it might be termed, found in both acromegaly, and gigantism, has been referred to. Garnier and Santenoise[41] have observed a case of gigantism associated with feminism, cryptorchidism, and polysarcia. Thoma[42] mentions having met with defective formation of the genital organs in a case of hemihypertrophy. In acromegaly, as soon as the changes in the bones become manifest, the secondary sexual attributes are changed. In the male the hair becomes scanty, while in the female hair is apt to grow on the face much as it does after the menopause or in ovarian disorders. The larynx hypertrophies and the voice deepens. Infantilism and hypoplasia of the genital organs have also been observed in cases of tumor growth in the pituitary in the absence of signs of acromegaly. Some years ago I performed an autopsy on a woman about thirty years of age who had a perithelial sarcoma of the pituitary without signs of acromegaly, in whom the genital organs were markedly undeveloped. Babinski also reported to the Neurological Society of Paris (June 7th, 1900) the case of a girl of seventeen, who presented the signs of infantilism, amenorrhœa, abundant fat, scantiness of hair, but without acromegaly. She developed pains in the head with disordered vision, and epileptiform convulsions. After

death it was discovered that she had a tumor of the pituitary. It is clear then that there is some relationship between lesions of the pituitary and thyroid glands and genital disturbances. What, then, is the primary disorder which leads to such extraordinary anomalies of growth and development? Breton and Michaut[43] have suggested that there is a trophic deviation of the genital activity to the bone marrow so that the medullary bone-forming function preserves its activity indefinitely. The cessation of genital activity would lead to acromegaly. This view is somewhat similar to that promulgated previously by Freund, Klebs, and Verstraeten, who held that there is a disturbance of the evolution of the genital function. If genital evolution is in excess we get gigantism and acromegaly; if defective, we get infantilism and dwarf growth. It is, of course, well recognized that with the onset of puberty the efflorescence of the sexual characteristics is coincident with increased growth and development of the body as a whole. The operation of castration has been observed to exert a notable effect on the stature of the body as well as in inhibiting the development of the secondary sexual peculiarities. In eunuchs the height is often extreme. This is due chiefly to a disproportionate increase in the length of the legs. Lortet has confirmed this statement by an examination of the skeleton of an Egyptian eunuch 196 cm. high. In castrated animals, the capon and the ox, the same increased growth of the lower or hind extremities is to be observed. Silva[44] has further recorded a curious observation in a youth who was normal until the age of thirteen. The testes then remained atrophic and when about twenty he began to grow rapidly, eventually manifesting some enlargement of the head and extremities, muscular weakness, anosmia, slight scoliosis, to such a degree as to suggest acromegaly.

While such facts as those just mentioned are suggestive of some relationship between genital insufficiency and disorders of growth and nutrition, to my mind the evidence is not strong enough to induce us to accept the view that deficiency of the genital organs is the cause of these disorders. Two-thirds of the cases of acromegaly develop after puberty is practically reached. The loss of sexual power in the male is gradual and progresses *pari passu* with the extension of the disease itself. In the female, too, while amenorrhœa is a frequent and often the first symptom of the disease, it is not invariable. Again genital hypoplasia and other signs of infantilism are often present in dwarfs, and the argument might be applied with equal force to explain dwarfism. The same cause could hardly produce at one time dwarfism and at another gigantism. Moreover, while genital hypoplasia has been often observed in cases of thyroid atrophy and gross lesions of the pituitary body, so far as is known castration does not produce a converse effect on these particular organs. While, then, genital hypoplasia undoubtedly plays some rôle in osteogenesis, it seems to be quite a subordinate one, and appears to be inadequate to explain the more marked aberrations from the normal path of development. The functions of the thyroid gland, the pituitary body, and the sexual organs are, however, no doubt correlated, and it is probable that the normal course of growth and development is dependent on a certain balance of power exerted by these glands. Of what nature is this correlation we are to a great extent in the dark. It is generally believed that the glands mentioned produce internal secretions that are essential to the normal course of the metabolic processes. The evidence in favor of this is less strong in the case of the sexual organs (testes and ovaries) than for the other organs. It may be inferred that while the metabolic processes referred to are vital in nature, they are inextricably associated with chemical transformations. The importance of chemical substances in the growth of the organism is well illustrated by the experimental work of Wegner, Maas, and Gies.[45, 46, 47] Wegner proved that by feeding rabbits with minute doses of phosphorus for a prolonged period he could get a marked increase in the formation of bone at the epiphyseal sutures of the long bones. The same thing has been found to occur with arsenic. Observations upon the nature of the metabolism in giants are hitherto lacking, but we have considerable evidence to show that in acromegaly metabolism is disordered. There appears to be a tendency to an overproduction of lime salts in acromegaly. Deposits of lime have been found in various parts of the body, especially in the pituitary, the thyroid, and the vessels (arteriosclerosis). Ossiform infiltration of the dura mater has been observed. Von Moraczewski[48] has also demonstrated a tendency to the retention of lime and phosphorus in the system in cases of acromegaly. Not only then is there an increased deposit of lime at the extremities of the bones, but also in widely distant parts of the body.

We are, I think, led to the inevitable conclusion that gigantism, like acromegaly, is very often a disorder of development brought about by abnormal metabolic processes. We must also admit that a large proportion of cases of gigantism are etiologically the same thing as acromegaly, and that an additional but uncertain number are probably abortive acromegaly (acromégalie fruste). One consideration must, however, be by no means overlooked in any discussion of the question of internal secretion. The doctrine of internal secretion as at present understood implies the existence of certain substances in the body upon which the secretion of the glands in question may act. Now the gland, thyroid or hypophysis, may be totally unable to perform the duties required of it, owing to some lesion, or it may be only relatively so. In either case similar symptoms would arise. This doctrine of relative inadequacy has been advanced by Prof. J. G. Adami,[49] and has by no means attracted the attention it deserves. On the one hand, relative inadequacy of a gland will set in as soon as its reserve power has been exhausted, and may increase until it becomes absolute. On the other hand, there may be an excess of the substances upon which the internal secretion is supposed to act. Therefore it is quite possible that certain forms of developmental disorder may be due to relative inadequacy on the part of some of the important glands, that, as we have seen, are competent to modify nutritive processes. In the case of gigantism, relative inadequacy of the pituitary, or it may be a relative overadequacy, short of producing the regular symptoms of acromegaly, might influence growth so as to bring about excess.

However this may be, and the deduction is alluring, there still remains some small proportion of cases of gigantism which cannot be explained on any of these theories. Such are the cases in which in addition to excessive height there is great strength with perfect proportion. Here there can be no question of disease in the ordinary acceptation of the term. Such giants are examples of the so-called "athletic" habit of body, and are strictly comparable to the giant infants before referred to. They represent the structure of the human body carried to its highest point. They may be regarded as examples of *true* or *essential* gigantism. Infantilism and pituitary dyscrasia cannot explain them. Rather are they to be referred to peculiarities inherent in the germinal cells of the progenitors. This view is supported by the fact that certain anomalies, for example polydactyly, malformations of the genital organs, and congenital hydrocele, are apt to be associated with the increase in size and weight.

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HÆMOLYSIS.—(Synonyms: Hæmocytolysis; Hæmatolysis; Laking of blood; Globulysis; Erythrocytolysis.)

Although etymologically this term includes destruction or solution of both red and white corpuscles, yet by usage it has come to be applied, when used without specification, only to the erythrocytes. When corresponding changes of the leucocytes are considered, the specific term *leucolysis* or *leucocytolysis* is generally used. In this article the term hæmolysis will be used, as above indicated, to apply only to *erythrolysis*.

In hæmolysis the essential phenomenon consists in the escape of the hæmoglobin from the stroma of the corpuscles into the surrounding fluid. As it is not exactly known in what way the stroma holds the hæmoglobin normally, whether purely physically or in part chemically, or whether the stroma consists of a spongioplasm or a sac-like membrane, or both, the ultimate processes that permit the escape of the hæmoglobin are not finally solved. However, the agents by which the escape is brought about are well known and extensively studied, and they are found to be of extremely various natures. They may be roughly classified as: (1) Known physical and chemical agents; (2) unknown constituents of blood serum; (3) bacterial products; (4) certain vegetable poisons; (5) snake venoms.

While the known chemical and physical agencies in the production of hæmolysis have much significance in physiology, and to some extent in pathology, yet the importance of the subject of hæmolysis at the time of this writing rests chiefly upon the work now being done with blood serums; and in turn the chief importance of this work lies in its relation to problems of bacterial destruction, cell destruction, and the general laws of cell susceptibility and cell resistance. Hence we shall devote particular attention to the subject of serum hæmolysis, appreciating that whether time does or does not show this work to be of as far-reaching importance as is now hoped, yet in any event it will mark a distinct period in the history of medical science. As being by far the simpler, however, we shall first discuss:

(1) Hæmolysis by Known Chemical and Physical Agencies.

If distilled water is added to corpuscles of any kind, osmotic changes are bound to occur, since within the cells are abundant salts, soluble in water, which will begin to diffuse outward in an attempt to establish osmotic equilibrium between the corpuscles and the surrounding fluid. Conversely water enters the corpuscles at the same time, and accumulating there leads to swelling until such injury has been produced as permits the hæmoglobin to escape and enter the surrounding fluid. Before this occurred the fluid was opaque because of the obstruction to light offered by the red cells. The stroma now settles to the bottom, while the hæmoglobin diffuses into the fluid, making it red, but perfectly transparent. This process has long been known as the "laking" of blood, and is essentially the condition present in all forms of hæmolysis. That the hæmoglobin escapes only through injury of the stroma and not through simple osmotic diffusion is shown by the fact that if salt solution of the same concentration as normal serum is used instead of distilled water, no such escape of hæmoglobin occurs. As hæmoglobin is perfectly soluble in the salt solution it should pass out if it diffused as do the salts. Since there is no escape of hæmoglobin in such a salt solution, it is evident either that the stroma is not permeable to hæmoglobin, or else the hæmoglobin is in some way attached to or combined with the stroma. Again, if the corpuscles are placed in a solution of salt more concentrated than their own fluids, water escapes and the corpuscles shrink; as no hæmoglobin escapes with the water it is evident that the stroma is not permeable to hæmoglobin when intact. Therefore it would seem that hæmolysis by distilled water may be purely physical, produced by the cell stretching until rupture occurs and the hæmoglobin escapes as from a sac, or else it may be that the stroma is partly soluble in water but not in salt solution, so that the distilled water dissolves the stroma and the hæmoglobin escapes from its attachment. Because of the resemblance of the process of hæmolysis to the rupture of plant cells with escape of their contents when they are placed in distilled water, it might be assumed that hæmolysis is largely a physical matter, but there are many indications that chemical changes must be involved. For example, if a red corpuscle in an isotonic solution is cut into pieces the hæmoglobin does not escape, indicating that its structure is quite dissimilar to that of the simple vegetable cell, and that there is some union of stroma and of hæmoglobin other than physical.

Repeated alternate freezing and thawing is another physical means of bringing on hæmolysis. Heating to 62°–64° C. causes hæmolysis of mammalian corpuscles; in cold-blooded animals this seems to occur at a slightly lower temperature.

Some chemical agents, as might be expected, are capable of liberating hæmoglobin, even when the corpuscles are in isotonic solutions. The ordinary salts of serum, of course, do not have this property, but ammonium salts are strongly hæmolytic. Urea also will dissolve red corpuscles. The chemical agents that dissolve red corpuscles seem to be those that have the power of penetrating the stroma. Ammonium salts and urea penetrate the corpuscles freely and cause hæmolysis. Sugar and NaCl seem not to penetrate the corpuscle, and therefore do not produce hæmolysis. Of the permeating substances there seem to be two types: One, like urea, does not produce hæmolysis when in a solution of NaCl isotonic with the serum; the other, like ammonium chloride, is not prevented from producing hæmolysis by the presence of NaCl. All these agents seem to effect hæmolysis by acting on the stroma, for when the stroma of corpuscles