1938

Acromegaly

W. E. Holmes
University of Nebraska Medical Center

ACROMEGALY

by

W. E. HOLMES

SENIOR THESIS

Presented to

THE UNIVERSITY OF NEBRASKA

COLLEGE OF MEDICINE

April 1938

TABLE OF CONTENTS

BIBLIOGRAPHY

INTRODUCTION

In recent years the pituitary gland and its functions have attracted increasingly more attention in medical circles. The fact that these functions have such widespread effects on other body functions makes it evident that such studies are very enlightening and may offer much in the knowledge of certain conditions which have heretofore seemed refractive to explanation or treatment. Therefore it behooves the modern medical man to recognize this gland as a vital part of the endocrine system and acquaint himself with developments in the understanding of its functions.

In this paper we shall limit ourselves to thee growth promoting hormone as it manifests itself in the syndrome known as acromegaly, and some of the characteristics of the disease itself together with the theraputic measures which are useful. What is believed to be a representative portion of available literature on the subject has been used as authority for the material presented.

HISTORICAL SUMMARY OF ACROMEGALY AND THE GROWTH HORMONE

The disease here under consideration has been shown to have so close a relation to the anterior lobe of the pituitary gland and the hormone secreted there which has to do with the regulation of body growth that it seems proper to consider these aspects as important factors in the development of our present understanding of the disease process.

The pituitary gland has been described anatomically in some of the oldest literature. It was thought by the Greeks to be an appendage of the nasal mucous membrane. To it they ascribed the function of a mucous secreting gland, the products of which served to lubricate the nasal passages. Further attempts to describe the gland were not made for many centuries (Cushing[16]).

The work of Rathke (1838) and Gotte, Mikalkovics and Balfour (1874) is also reported by Cushing[17]. Rathke described the pouch which now bears his name and found that it formed part of the gland structure. He thought, however, that the structure was derived from the foregut and accordingly ascribed to it an endodermal origin. His treatise was elaborately written and based upon extensive studies of embryos.

Gotte, Mikalkovics and Balfour made further

studies on this structure and found that it was derived from the cells of the dorsal part of the primative buccal cavity. These writers also recognized the neurogenic nature of the posterior lobe of the gland. Their studies, together with those of Rathke, are classical descriptions of the anatomy of the gland to which very little of fundamental importance has been added, aside from certain histological staining properties.

We shall, therefore, leave for the present the anatomical considerations and turn to the early descriptions of acromegaly. Marie[48] described the disease entity in some detail. He did autopsies on several patients with definite acromegalic tendencies and found, aside from the superficial characteristics (enlargement of the digits, prominent mandible, supraorbital prominence, coarse features, thick lips and tongue, enlarged joints, etc.), a generalized increase in the size of body organs. He also noticed that about half the cases showed enlargement of the pituitary body with definitive neoplastic characteristics. He attached no special significance to this finding, however, and thought it to be merely a part of the disease process.

A dystrophy, analogus to myxedema, was also

described. This, he thought to be due to diminution or complete loss of function of the pituitary gland. At about the same time Vessale and other pathologists[17] described hyperplastic processes with similar findings in the pituitary and other body organs, but did not give special significance to the pituitary findings. They did, however, think all of these changes to be due to a metabolic disturbance of unknown origin.

No experimental approach was attempted until Sandri[60] fed large quantities of anterior pituitary substance of the ox to young mice. His experiments were carried on without any definite suspicion of the relation between acromegaly and his work. He found a rather marked arrest in growth. The same result was obtained by injection of an emulsion of the gland. Crow, Cushing, and Homans[15] prepared a boiled suspension of the anterior lobe. The injection of this caused immediate loss of weight both in puppies and in grown dogs. These men also attempted hypophysectomies but most of their dogs died of post-operative complications before any convincing results were obtained from the experiments.

Schafer[66] fed pituitary to white rats and found little or no effect on their growth or metabolism.

This work prompted Aldrich[1] to conduct further feeding experiments in an attempt to confirm or disprove the findings stated above. He added 50 to 75 mgms. of fresh dessicated, defatted anterior lobe of the ox to the diet of young dogs. After about eight months of such feeding he concluded that their growth was certainly not impeded but did not show any stimulation of growth as measured by increase in body weight. He thought that in some individual instances, stimulation did occur. He, therefore, performed further experiments on white rats[2] and decided that anterior lobe feeding did not increase the rate of growth and seemed to impede it.

By 1913 the theory of endocrine secretion of glands had become reather definitely established, and Haliburton[33] made application of this theory in his handbook of physiology in which he said "The anterior lobe of the pituitary consists of large granular cells and numerous blood vessels. It's precise function is not determined, although probably it is a vascular gland pouring an internal secretion into the blood which influences growth. Abnormal hypertrophy is associated with acromegaly..... Feeding young animals on the gland hastenes the growth of their skeletal structures."

His views were based, for the most part, upon

experiments conducted in Spreckles laboratory at the University of California. The earlier work was done on young fowles and was reported by Wilson[71] in 1914. Ox pituitary was used and again retardation of growth was found.

Later Robertson and Burnette[59] from the same laboratory included studies on anterior pituitary feeding in very extensive studies on growth in general. Their first reports of stimulation of growth had to do with the marked increase in the rate of growth of carcinoma in white rats. The rats were inocculated with the tumor and pituitary effect observed at various stages in its development. The amount of acceleration was found to be relatively greater in small tumors than in larger ones. These experiments were carefully controled by observation of litter-mate series of animals similarly inocculated without any treatment and other series in which emulsions of liver tissue were injected.

Aldrich[2] had suggested a possible preliminary inhibition of growth followed by stimulation in experiments carried over a longer period of time than were his first studies.

Robertson's above mentioned experiments confirmed the preliminary slowing effect followed by stimulation of growth. He recognized this only, however, when the pit-

uitary substance was included in the diets before the thirtieth week of life. If the treatment was begun after that time no change whatsoever in the weight of the mice was observed. Neither could he find any change that he was able to measure in the metabolic processes, structure, behavior or life span of treated animals.

Large numbers of experiments with pituitary feeding were performed after 1913 on various animals. An example of these studies was found in Clark's[13] work at the Oldham Farm in Port Hope, Onterio. He caused an increase in egg production in hens fed with anterior pituitary substance and at the same time observed an increased fertility of the eggs as evidenced by hatch percentages. Such experiments have considerable interest but do not materially add to our information regarding the true nature of the gland so no further reference will be made to them.

The problem of pituitary dwarfism is also of some interest here, especially as a counterpart to the increased secretory activity with which we are dealing. This was studied by preventing the development of the anterior lobe by Smith[67], another worker in the University of California biological laboratories. He selected tadpoles for his experiments and devised a technique which enabled him to destroy the anlage of the anterior lobe before it reached the state of functional adequacy. His first

reports of these experiments were published in 1916, in a rather lengthy paper describing his technique in detail. He destroyed Rathke's pouch during the time when it was still a definite appendage of the buccal cavity. The tadpoles so treated showed very definite differences from the normal individuals. They grew very little though for a considerable period of time they appeared to be in normal health and maintain normal activities. Metamorphosis in these individuals was never begun and they maintained the same light silvery gray color of skin throughout the period of observation. The untreated tadpoles grew rapidly, acquired the characteristic dark pigmentation of the skin and at the proper time began and completed their metamorphosis into adult frogs. He reported another similar series with the same results in 1917.[68]

Allen[3], at the University of Kansas, conducted similar experiments and found in addition to failure to grow and metamorphose and the lack of pigmentation, a marked lowering of resistance. Whether this was a result of the extirpation of the gland or not is somewhat questionable due to the fact that his tanks were not suitable to such experiments and the normal frogs died soon after metamorphosis had occurred. The work does confirm the relationship between the anterior lobe

and the growth processes in the young of this particular species. He continued these studies in 1920[4], doing experimental transplants of anterior pituitary tissue from adult frogs to the hypophysectomised tadpoles. This resulted in a resumption of growth and development. It seems that these are some of the most conclusive evidences of the relationship of anterior pituitary to growth which had been published at this time. They were so carefully controlled and the results were so definite that there can be no doubt of such relationship.

After the above mentioned experiments were reported other workers found frog larvae to be very convenient and profitable subjects for experiment. Hoskins and Hoskins[34] found a relationship between the pituitary and thyroid glands. Their tadpoles, from which the thyroid had been removed, failed to metamorphose. They found, however, that the removal of the thyroid apparently caused some increase in the rate of growth of the tadpoles which could be compensated by a feeding of thyroid or hypophysis. Postmortem dissection of hypophysectomized tadpoles showed not only failure of the thyroid to develop properly but an apparent degeneration of the existing parts of the gland. This condition could also be prevented by feeding anterior pituitary. Such feeding further stimulated growth but metamorphosis did not occur. In these

experiments we see not only confirmation of definitive growth stimulating function of the anterior pituitary but also of an interrelationship between it and another gland of internal secretion, the thyroid. Here again, it becomes necessary to limit our consideration to the functions of the pituitary in view of the fact that a vast amount of information has been accumulated concerning relationships with other glands of internal secretion. This material is very interesting and must be included in any adequate consideration of the function of the anterior pituitary gland, but at present we are concerned primarily with only one of these functions.

Other endocrine functions may be involved here, however, when tumors are present that cause pressure on other parts of the gland and resulting loss of function of those parts. Evans and Long[24] have done an enormous amount of work in this connection and have shown such relationships in animal experimentation on normal individuals as well as the disturbed relationships of oestrus, menstruation and pregnancy. Through their work and that of Putnam, Teal and Benedict[53] the various hormones of the pituitary have been differentiated to a large extent. They have also furnished a large part of the foundation for recent work disclosing certain antagonistic characteristics of the various hormones. This has resulted in the

modern conception of the pituitary as the master control of these functions.

Evans, Simpson and Cornish's[26] isolation of a definite hormone secreted by the anterior pituitary which is capable of stimulating growth without the effects on other glands and functions will be discussed later. For the present we will postulate the existance of such a substance and eliminate from discussion the widespread effects of pituitary secretion in general.

Uhlenhuth[71] recognized the role of the gland in growth stimulation during the normal growth period of life and believed that it did not cause further growth after this period. He based his conclusions on experiments with metamorphosed salamanders which were fed a pure diet of earth worms. The rate of growth of experimental animals greatly increased and they continued to grow beyond the limits of normal size producing giants. This finding could not be demonstrated in those animals which had attained their full growth. Thus we have seen a complete change in results of experiments involving the pituitary from those first discovered.

Scott and Broderick[65] were the first to recognize definitely the application of this principle in humans. This, of course, was a consideration in all experimental work mentioned so far but there had not been sufficient

evidence established to allow for even theorization on the probable clinical manifestations in man. These men, however, did make the application and after observing patients with what they considered a pituitary deficiency, they made the following observation: "We see children developing in a hesitating way, both in mind and body, not going straight. We are apt to think of it as a character deficiency or we call it laziness or willful stupidity, but it is nearly always an endocrine deficiency"

They suggested the use of the gland in senile epilepsy without giving any indication of the basis of their treatment. They also thought that such treatment might offer relief from a condidion which similates the cachexia which follows removal of the pituitary gland.

Extraction of the active principles of the anterior pituitary had long been a problem which baffled experimenters. It was not until 1921 that Evans and Long[24] successfully accomplished the extraction of a solution which would produce noticeable effects consistantly. Their method was relatively simple. The principle step involved was a primary extraction in 30% alcohol. This was rinsed through Loke's solution and titrated through sand before being centrifuged. The supernatent fluid was used for injection, controls being injected with similar substances from liver. The dosage of this solution varied from

1/8 to 1 cc. depending upon the age of the animal. The rats used were pure strains and litter-mates were used as controls in the experiments.

An increase in the weight of experimental animals was found together with lengthened oestrus cycle. The animals received some toxic effects from injections but increased in weight more rapidly than their litter-mates in spite of this reaction.

Putnam, Teal and Benedict[54] designed a more elaborate method of preparation of a similar extract and succeeded in overcoming the obstacles which had previously prevented the production of sterile solutions. They found that heating destroyed the active principle. Their next thought was the addition of an antiseptic which would be harmless to the animal into which it was injected or to the principle itself. Alcohol, phenol, mercurochrome, acroflavine and hexyresorcinol were tried but when used in effective concentrations they all precipitated and destroyed the hormone. Another perplexing problem was preservation of the hormone in solution. Sodium benzoate in ½ to 1% solution was found to keep the substance in sufficiently good condition for one week in an ice box and for several months in frozen. This solved the problem of preservation but they were forced to resort to filtration methods to remove bacteria from the solution.

Ordinary filtration material was not adequate, becoming clogged very readily by the cloudy, thick solution. Mindful of the danger of adsorption the Burkefeld filter was used but was slow and only about 50cc. per day could be produced. The filtrate, however, was found to contain the hormone by experiments with rats. Finally the Shieck filter was employed which, with the use of suction gave a clear sterile solution. This also clogged after a time but was quite satisfactory.

This solution was proven to contain growth stimulating substance in experiments with rats and dogs. The report also included the treatment of one human patient suffering from pituitary insufficiency associated with craniopharyngioma. Slight reaction from the injections was observed but some of the systemic symptoms were relieved after each injection. The patient eventually died of the tumor and no harmful effects from the extract were described at autopsy. Thus we see the foundation of the postoperative treatment of tumors of the pituitary which is so often necessary in acromegalics from which such tumors have been removed.

The extract prepared by Putnam, Teal and Benedict[54] as described above was used in their classical experiments using bull dogs. Two pedigreed female litter-mate dogs, age 4 weeks were used. Experiments were carried on for

fifteen months. At first the experimental dog increased greatly in size, maintaining about normal proportions. Later, however, changes became evident which were very characteristic of acromegalic tendencies and these changes progressed to a very advanced stage. The presence of the sex fraction in the extract was evidenced by the fact that the treated dog went into heat after 12 months of treatment and the secondary sexual characteristics were very marked as compared to the other dog. The control never went into heat.

We have here definite indication of the two phases of activity of the growth hormone. The first is the stimulation of what appears to be normal growth, and the second the production of acromegalic characteristics after the normal growth period has ended.

More refined methods of preparation have been developed by Evans and others together with more or less acurate means of standardization. The significant thing in this work is, however, the demonstration of the relationship between the pituitary growth hormone and acromegaly.

Many cases have been studied and reported and much learned about the disease but certain phases still remain somewhat of a mystery as we shall see later.

ETIOLOGY

We have seen in our historical review that a great deal of work has been done on the effect of the growth hormone of the pituitary on the development and size of individuals. Many workers have treated dwarfism with the extract of the gland containing the hormone with quite gratifying results; enough so that we may feel justified in the conclusion that deficiency results in slow growth of children.

In acromegaly we are apparently considering a disease characterized by a marked increase in growth which involves at various times, all the tissues of the body. It was this observation which probably lead early workers to suspect a hormonal agent as causing the changes seen. Various men had suggested a pituitary hormone in view of the frequency of pituitary adenomas in acromegalics. After Putnam, Teal and Benedict prepared[53] a fairly concentrated extract of the hormone and performed their classical experiments on bull dogs[54] in which their photographs and measurements show a very accurate experimental acromegaly by injection of this hormone, there remained little doubt as to the causative agent.

AGE OF ONSET

Experiments have shown that excesses of the hormone

early in life, before the fusion of the epiphyses of the bones, caused stimulation of growth in what appeared to be a uniform and proportional manner and resulted in individuals reaching the proportions of giants. Certain early writers report cases of acromegaly in children but many of these are questionable and seem not to be properly classified. Rake[55] described a case in a negro ten years old who was very large for his age but his photographs do not show convincing acromegalic changes in the hands and feet.

The exact time of onset in a given individual is rather hard to determine due to the insidious appearance and gradual progression. Many patients are not aware of any abnormal changes until their attention is attracted to it by friends or until the changes are very marked and the disease of long standing.

For the same reason it is difficult to elicit from patients, once they have consulted a doctor, just how long the changes have been taking place. Workers at the Peter Bent Brigham hospital[16,17] have taken special pains to obtain this information and apparently the third decade of life is the most frequent time of onset. Certain other cases, no doubt, have some similar pituitary pathology earlier than this but such patients have the characteristics of giants with a superimposed

acromegaly.

Apparently there are no authentic reports of infantile acromegaly the truly characteristic disease appearing after completion of growth.

RACE

The disease seems to occur in practically all races. The only apparent special suceptibility is that mentioned frequently in Jews. Lorand[19], in his discussion of the relative frequency of diabetes in Hebrews, mentions a similar frequency of acromegaly.

Davidoff[11] found 21% of the patients he reported in 1926 to be Jews. This seems to be significant since the census of 1920 showed only 3.4% of the American population to be Jewish. He also reported cases in individuals of English, Irish, German, Scandanavian, Italian, French, Spanish and several other nationalities but none of these could be shown to have any special significance. Other reports show the Negro race to be susceptible but not outstandingly so.

SEX

Various series of cases show somewhat different relationships as regards the incidence in males and females, but in general they present the symptoms about equally and no predominence can be shown in either sex.

OCCUPATION

Neither can any evidence of definite relationship be established between occupation and acromegaly. From time to time writers have suggested the possibility of the relationship between nervous tension and endocrine disturbances. This idea has been correlated with apparent slight predominence in members of the professions and skilled trades.

FAMILY HISTORY

Davidoff[20] reports four cases where blood relatives showed the disease (one brother, one sister, one uncle, and one aunt). About half the cases reported from the Peter Bent Brigham hospital seem to show a family history of endocrine, metabolic, nervous or mental disease when accurate and complete histories are obtained.[18-19-20] At present, records are far from adequate to show that the disease is inheritable according to the Mendalian law but indications seem to point to some family tendencies to endocrine instability.

PAST HISTORY

In practically all cases the past history of disease in acromegalics includes very little that can separate it from the history of illness which might be expected in normal individuals. Many writers have

attempted to correlate fevers, shocks and other serious diseases findings are not conclusive. Typhoid fever has frequently been accused but no proven correlation has been found.

Thus the disease is seen to be a constitutional deficiency possessed by certain individuals with possible familial and racial predispositions and caused by excessive secretion of growth hormone by the anterior pituitary gland or it's tumors.

SIGNS AND SYMPTOMS

The manifestation of pituitary disfunction, under consideration is, of course primarily a syndrome of skeletal and somatic overgrowth after a certain, and rather characteristic pattern. As we have seen the condition is a result of oversecretion of the growth-promoting factor of the secretion of the anterior pituitary body, and can be reproduced experimentaly by the methods described.

The gland may be implicated by what appears to be a physiological hyperfunction or there may be actual enlargement of the gland with microscopic evidences of increased acidophylic cells asuming the proportions of neoplastic change. Accordingly we must consider five groups of cases.

GROUP I. Cases with only the glandular symptoms

GROUP II. Cases with glandular symptoms and local symptome.

GROUP III. Cases with glandular symptoms and general pressure symptoms.

GROUP IV. Cases with glandular symptoms and focal signs.

GROUP V. Fugitive acromegaly.

In the first group we see the progression of symptoms which truly characterize the disease. These have to do with hypertrophic changes of the

skeleton, its coverings and the body organs. The skeletal aspects are those which were first described by Marie[16] in his first account of the disease. When two of these patients came to autopsy, Broca[16] reported the presence of definite viceromegaly.

Cushing[17] in his descriptions of pituitary disfunction, described and classified the symptoms at considerable length. In most cases the progressive enlargement of the hands and feet was the first indication of the onset of the disease. This continues as further symptoms appear and forms a prominent part of the entire picture. It results, from enlargement of the articular portions of the bone in deformities of both position and limitation of motion. Patients are frequently unable to close the hand sufficiently to perform ordinary grasping activities. This bony overgrowth also involves other bones but is more evident about the epiphyses, thus manifesting itself as more of less generalized enlargements of joints. This same process may extend to the joints of the vertebral column and result in fixation and curvatures. Most frequently scoliosis and kyphosis are seen (Cushing[17]).

This skeletal enlargement results in an increase in size of the entire body framework including height to a certain extent. Cushing's[16] later work describes

cases in which the height of the individual was increased from 2 to 4 inches. The characteristic protruding jaw is a manifestation of the same process but seems to be one of the most frequent symptoms observed. It is accompanied by coarse features, thick lips and tongue. Accordingly the patients often have a rather characteristic speech with loss of resonance and a thick, gutteral tone. When a great deal of enlargement of the mandible occurs there is frequently an increase in spacing of the teeth. This occasionally occurs in the maxillary bones and the teeth there are similarly affected.

Nasal obstruction due to hypertrophied bones surrounding the air passages was reported by Cushing and Davidoff.[18] Marked increase in the circumference of the chest also frequently accompanies the disease.

Associated with these skeletal changes there is overgrowth of soft tissues. The muscles increase in size and in earlier stages the strength of the individual is markedly increased.

The behavior of these patients is usually considerably changed with the progression of the disease. They tend to become awkward and though for a time are more powerful than before there is apt to be a mental and physical lethargy. The endurance of the individual

is definitely diminished and patients tire more easily though they may be able to exert more energy after a period of rest. The reaction time of the entire voluntary muscular system seems to be diminished.

The skin is moist, soft, and elastic and does not have a stretched appearance in spite of the enlargement of the underlying structures. There is a tendency toward increased pigmentation of the skin. The complexion is darkened as is very frequently the color of the hair.

Visceral enlargement is usually not so definitely observable by physical examination. This might be expected in view of the diffuse hyperplasia observed. The most commonly seen evidence of this process is the enlargement of the spleen.

Atkinson[5] reviewed a series of fourteen hundred cases and found the generalized visceromegaly mentioned by Broca in only 46 cases. This condition is not found, under any other circumstances, however. Roberts, Camb and Lond[59] reported a case of this enlargement of organs which they studied by X-ray (stomach, small intestine, colon, spleen, liver and heart). Strictly speaking visceromegaly should be considered as a term used to apply only to a condition of enormous enlargement of the viscera beyond all proportions to the size of the body. Propor-

tional enlargement of these organs, as evidenced by their weight at autopsy, is seen quite frequently. A table of their comparative weights is incorporated in the discussion of the pathology involved.

Laboratory signs are not particularly constant. The urine, in general, is negative. Some observers have described cases with glycosuria. Ellis[22] reports a case of his own in which there was a two plus sugar reaction in the urine. This patient had shown acromegalic symptoms for seven years. He was thirsty also and had a definitely increased appetite. Large appetites are the rule, however, rather than the exception. The patient showed a glucose tolerance curve characteristic of diabetes mellitus and insulin reduced the blood sugar and made the urine sugar free. This particular case had an acidophyllic adenoma of the pituitary which was successfully removed surgically. After this the blood sugar which had previously ranged from 100 mgs percent to 140 dropped to normal and the glycosuria disappeared. Later determinations showed a diabetic glucose tolerance curve, however, and an associated diabetes cannot be entirely excluded though removal of the pituitary factor resulted in definite improvement of this phase of the picture. Ellis was able to find twelve reported cases of acromegaly which had this sym-

ptom but they were not studied adequately enough to eliminate diabetes as a cause.

Evans, Meyer, Simpson and Reichert[25] were able experimentally to produce 4-plus urinary sugar and a blood sugar of 232 mgs percent in dogs by the injection of anterior pituitary growth hormone. This seems to indicate the association of this finding with acromegaly. They further associated it with the increases susceptibility of acromegalics to infection.

Schrire[64] studied the creatine and creatinine out-put in the urine and found a tendency toward increase in the excretion of these substances and decreased tolerance to them when administered by mouth.

A large percentage of cases reviewed showed decrease in metabolic rate when such was studied, and Rowe[57] conducted a series of careful measurements on a group of acromegalics and found, after cirrection had been made for temperature changes, a consistant lowering in the BMR. The average in cases studied was about a -22%.

Amenorrhea is a common symptom in women and appears quite early in the disease. Impotence is also found in men but does not appear except in the more advanced stages (Lackey[43])

X-ray studies of the pituitary fossa show little

or no variation in these cases aside from some thickening of the sella turcica compatible with the general bony hypertrophy.

In group two we find cases with the glandular symptoms associated with local subjective and objective signs. Headaches are very common. They are usually bitemporal in nature and often very severe. Associated with these headaches there is no increase in spinal pressure (Cushing[7]). The cause is not well understood but it has been thought that they are due to tension on the capsule of the gland. There may be an associated photophobia and some patients complain of discomfort in the deep orbital and increased sensitiveness of the eye to pressure.

X-ray of the sella showes three types of deformities: (1) that associated with thickening of the clinoid processes and dorsum ephippi, (2) that with thinning from pressure absorption of these parts, (3) that with more or less destruction of all outlines. The first group probably represents bony thickenings as a feature of the tendency toward osseous over growth , but is accompanied by an increase in the size of the pituitary fossa. The second group represents bony absorption due to pressure from a larger tumor mass and is an intermediate stage between the first and third. In the third stage the tumor is of such size that the contour of the sella has

been completely destroyed. This does not necessarily presuppose erosion of the capsule of the tumor.

In the third large group of cases, namely those with glandular symptoms associated with general pressure symptoms, we must presuppose a tumor of sufficient size to result in changes in the function of the cerebro-spinal fluid. The result is either an increase in the amount of fluid secreted by irritation or an obstruction of the normal flow. In the former case evidence of the increased pressure can be measured directly by spinal puncture. In the latter it is sometimes necessary to base an impression on the relative degree of variation of pressure by jugular compression.

Consideration must always be given in these cases to the possibility of some other tumor or cystic formation existing at the same time and causing the symptoms. Headache may be the only symptom; for vomiting, which is an inconspicious feature of many intracranial tumors, is particularly unusual in these patients. Certain physical signs are helpful, however. Among these are extracranial evidences of venous stasis, shown by fullness and tortuosity of the palpebral as well as the larger veins of the scalp. X-ray shows deformity of the sella consistently in these patients and also pressure enlargements of diploic channels.

Group four with glandular symptoms and focal signs is a small group as regards the number of cases included here exclusively. Many of the cases in groups two and three show focal symptoms. Practically the only common nervous indication is that associated with the optic nerve. Patients may complain of partial or complete blindness. Limitation of the visual fields often may be discovered on physical examination. The most frequent finding is the bi-temporal hemionopsia. This is, of course, associated with pressure atrophy of the central fibers of the optic chiasm. The blindness may be partial or complete depending upon the size of the tumor. With larger tumors the outer fibers of the chiasm may be involved producing complete blindness or one sided involvement causing total blindness in one eye only.

Any variation of these findings may be seen depending upon the various configurations of tumor growth. The optic atrophy is seen at the nerve head on ophthalmoscopic examination. Choked disc is also seen in association with general increase in intracranial pressure.

Shelton and Cavanaugh[***] considered the symptoms of stiff neck and loss of deep reflexes as focal signs in a case with very acute onset of pressure symptoms.

Group five includes cases characterized by a rather bizarre series of symptoms which seem to represent a reversal of pituitary function. In the early stages, these cases show evidences of acromegaly but these are replaced later by the phenomena of cachexia, weakness, increased carbohydrate tolerance etc. which were thought by Baily and Cushing[6] to be due to the "failure of the acidophylic cells". They called this syndrome fugitive acromegaly. It must be differentiated from the more frequent and usual course of the disease which includes the symptoms of pituitary deficiency later. In the condition mentioned above these symptoms occur relatively early, usually before the acromegalic changes have progressed a great deal.

Shelton, Cavanaugh and Patek[66] studied this further and reported several cases, the following of which is rather characteristic. The patient, a male, age 28, former medical student conplained of a sudden onset of severe throbbing headache and loss of vision. For two years previous to the onset of these symptoms he had noticed gradual enlargement of the hands which had assumed characteristic spade-like appearance of acromegaly. On physical examination opisthotinus, occular neuritis and loss of deep reflexes was found. In the

ensuing two years the headaches persisted but with less severity, the patient remained mentally alert but developed a tendency to asthenia and somnolescence. Libido and potentia remained unimpaired. There was no change in emotional responses or disposition, and there was no further progression of the acromegalic tendencies. Further study showed a high glucose tolerance, low BMR (-30 to -40) and the presence of a calcified shadow within the sella.

These latter symptoms and findings were interpreted as signs of pituitary insufficiency and therapeutic test substantiated this view. Alkaline extract of anterior pituitary gland was administered. The patient immediately showed a weight gain, having lost 60 pounds in the preceeding two years. When the treatment was discontinued there was an immediate loss of weight. During treatment the patient showed an increase in strength, decreased glucose tolerance and an associated increase in appetite. Blood pressure was not affected at any time. Corey and Graham[14] reported a case with similar progressing of symptoms after a tumor was removed surgically from the sella, there having been acromegalic tendencies before removal.

In this syndrome of fugitive acromegaly the appearance of symptoms of pituitary deficiency marks

the end of acromegalic progression.

Signs of pituitary deficiency are quite constant features of late acromegaly in which intercurrent disease has not ended fataly. There is a definite reversal of processes, the patients become weak, easily tired, lose weight, sometimes very rapidly to the point of emaciation, and they tend to increase mental dullness. This is the phase of the disease which is usually referred to as pituitary cachexia.

A similar condition may exist after destruction of the gland therapeutically. Corey and Graham[14] have described this in some considerable detail and point out that practically the same circumstances are found in pituitary deficiencies where the growth hormone is involved even though not preceded by acromegaly.

PHYSIOLOGY

Very little has been writen on the mechanism of the action of the growth promoting hormone. Many elaborate works on the end result of these processes are found but few attempt to explain them; whether they are direct or indirect (executed through the other endocrine glands or physiological processes). Paal[52] in 1933 showed that bits of thyroid cultures in a fluid medium were stimulated to definitely more rapid growth by the addition of the thyrotropic factor of the anterior pituitary secretion, while the effect was not produced by folliculin, pituitrin or prolan. Here we see a direct effect on the tissue when isolated from the organism.

The direct action of the hormone on the tissues is not at all certain, however, in view of the work of Asher, Houssay and Gonzales (referred to by Evans[23]). These workers obtained from the thymus a substance known as thymocrescin which would increase the rate of growth in rats. They also find rather definite thymic atrophy after hypophysectomy. An increase in the size of the gland out of all proportion to other organs with the administration of growth hormone is shown by Kemp[36] in his experiments with littermate pairs of mice. This would seem to indicate some possible connection

between the thymus and the increase in growth, but lack of more evidence makes proof of the relationship impossible.

Lee and Schaffer[41] described the growth of twelve pairs of littermate rats treated with antuitrin G. He studied the behavior of these animals with particular reference to the nitrogen balance. The pairs of rats were fed exactly the same diets in exactly the same amounts. The excess gain of the treated animals over the controls was: "live weight, 531 gms., body length 15 cm." Other excess determinations were as follows : water 447 gms., ash 22.4 gms., fat -119 gms., fat free dry tissue 173 gms., nitrogen 22.5 gms., energy -341 calories. Nitrogen and ash balances were found to parallel closely the excess gain in weight. This is rather definite proof of the fact that there is an actual growth. We see here, also, an increased efficiency in the utilization of food eaten and that the increase in size is more than merely the direct result of the increased food intake which follows the increase in appetite of animals treated with the hormone.

Very little has been said to explain this. Certain work with the fractionation and recombination of the amino acids has demonstrated that there is a substance present in protein which is also essential to growth which will not occur without that substance.

Kingston and Schryver[38] devised a method which they called the "carbonate fractionation" by which rather pure solutions of amino-acids could be prepared. Caldwell[9,10] recombined these acids in approximately the correct proportions and fed them as a source of nitrogen to young rats but the rats did not grow. He found, however that when such diets were supplemented by the butyl alcohol-soluble portion of hydrolyzed casein, growth occurred.

This unknown factor was first separated by Windus, Catherwood and Rose[75] in 1931 but to the present time the chemical nature has not been determined. It cannot be said to have any relation to the growth hormone to any further extent than being one of the requirements for growth. Neither has this substance been associated chemically with the growth hormone.

The processes within the body which are altered by the injection of the hormone give some interesting information. Gaebler[30] found that the hormone caused a prompt and very definite drop in urinary nitrogen due chiefly to change of urea content. There was an accompanying drop in blood nitrogen. This seems to indicate an addition of nitrogen to the tissues but this addition may not be retained and the sudden gains in weight seen with injections are always lost when the injections

are discontinued. The loss seen here is also in the form of urea. Gaebler suggests from these observations that the gain may be only in "reserve protein" rather than actual increase in amount of permanent tissue. There is, however, definite tissue retention of nitrogen since other experiments showed simultaneously increased dietary nitrogen intake, urinary nitrogen decrease while the fecal nitrogen remained unchanged. Teal and Cushing[70] confirmed these findings and observed further that in fasting dogs whose blood nitrogen has reached the fasting level which remains constant for weeks at a time the growth hormone will produce a further distinct drop.

Changes in calcium and phosphorus content of the blood and tissues are very slight and inconstant.

In later experiments on dogs Gaebler[31] has found that there is a great increase in water intake and out put, there being, however, very little water retention. There was also an increase in heat production.

The possibility of an intermediate function of the thyroid gland was studied by Gaebler[32] in 1935. He found that thyroparaphyroidectomy did not materially increase heat liberation caused by anterior pituitary growth hormone. Also that the nitrogen retention was not significantly altered by it. In one animal where

there had previously been a very small effect, thyroidectomy was followed by a very marked response. These findings seem to indicate that the thyroid gland is not essential to the functioning of the growth hormone. Some animals fed thyroid together with hormone injections seemed to show a somewhat greater response. In this series, the water increase was found to be primarily a matter of water storage followed secondarily by diuresis as the intake curve rose sooner than did the volume output.

From this and other similar work it seems quite natural to believe that the action of the anterior pituitary growth hormone is chiefly upon the general tissue metabolism directly in so far as the thyroid and parathyroid glands are concerned at least, and also that the effects are not due entirely to the presence of a thyrotropic hormone which increases thyroid activity thus increasing metabolism.

Gaebler[29] also found that by feeding sugar in amounts proportionate to the increase in metabolic rate he was unable to prevent the increase in fat metabolism. This increased metabolic rate is a temporary finding and is not seen in giant rats produced by the action of the hormone.

The B M R was found to be decreased by Lee,

Teal and Gagnon.[47] The giants showed 629 calories per square meter per day while controls showed 805 calories. The significance of this finding is rather hard to evaluate since the energy involved in the production of the markedly increased rate of growth was not taken into consideration.

The work of Shrire[64] in 1937 has opened a new field of investigation into the physio-chemical nature of metabolism under the influence of the growth hormone. He found an increase in creatinine secretion after about 83% of the injections. Thyrotropic hormone caused increased creatine without significant effect on creatinine. Corresponding changes in tolerance to these substances was found following similar injections.

All this seems to leave the physiology of the action of the hormone under consideration something of a mystery with very little except the increase in tissue mass to show for its effects.

PATHOLOGY

The pathological considerations in this disease involve nearly all the organs and tissues of the body. The precise relationship between the pituitary and other organs is somewhat obscure in many cases and it is often very difficult to differentiate the changes for which the growth hormone is directly responsible from those resulting from deficiency of other pituitary functions or from indirect effects by way of other endocrine glands.

The considerations may be outlined as follows:

A. Anterior pituitary
    1. With tumor
    2 Without tumor

B. Other endocrine glands
    1. Thyroid
    2. Parathyroid
    3. Adrenals
    4. Pancreatic Islands
    5. Thymus
    6. Gonads

C. Skeletal Tissues

D. Somatic soft parts.

E. Viscera.

In discussing the hystopathological changes of the anterior pituitary we must first consider some special terminology which has evolved in descriptions of the cells found here. It may be well to include some of the normal histology as a foundation for pathological findings. The cells of the anterior pituitary are of polygonal form with generally sharply defined cell boundaries. They are arranged in columns between which are rather delicate vascular sinuses. The connective tissue support is composed of fine fibrous connective tissue which forms a rather inconspicuous part of the microscopic picture.

The types of glandular cells are identified by the type of granules present. There are two primary types, the chromophilic and the chromophobic. The former take ordinary stains well, the latter being characteristically refractive to such stains. There are also two types of chromophilic cells. These are known as acidophilic and basophilic. These terms were applied to the granules owing to the type of stain (acid of base) which colored them. Many such stains have been used but in general the basophiles are characterized by affinity to these stains. Many writers since the middle of the last decade refer to these as alpha and beta granules rather than designating them as above.

The types of cells in which the two types of granules are seen are apparently the same but one particular cell never contains both types of granules. Thus, the cells themselves are very often referred to as alpha or beta cells depending on the type of granules found in the cytoplasm.

Baily and Davidoff[7] described very acurately the characteristic changes seen in the alpha cell adenomata of acromegaly. They appear to be proliferative in nature and the cells then to lose their thick cord-like arrangement and become somewhat more tightly packed. The form and size of the cells is irregular and some of them are multinuclear. In active cases mitotic figures are frequently seen in varying numbers but evidences of amitotic divisions of the nuclei are also frequently seen. The alpha granules tend to be more numerous at the periphery of the cytoplasm and in general they are finer than in the normal cells.

The intercellular structure in the adenomata is also changed from that of the normal gland. The cells themselves are, of course primarily alpha granular. The connective tissue elements are usually decreased in active tumors but may tend to increase following degenerative changes of the glandular cells. Vascular supply in the normal gland is represented in micro-

scopical section by rather numerous and fair sized capillaries between the cords of cells. In the adenomata these capillaries are very indistinct and lack any orderly relationship to the cells of the tumor.

There are some special characteristics of these tumors which were studied by Bailey and Cushing[6] in 1928. They examined 100 cases most of which showed secondary pituitary deficiency following a definite course of acromegalic symptoms. It was their intention to discover, if possible, a correlation between the histological course within the tumor itself and the syndrome of symptoms which we have referred to as fugitive acromegaly.

To this end they set about to study first the tumors themselves as regards the variation in the relative proportion of cells with alpha granules to those where none of these were seen. After examination of material microscopically, the tumors were divided into six groups based upon these histological characteristics as follows:

Group 1. Here practically all the cells were packed with alpha granules. The cytoplasm was relatively clear and nuclei showed some mitotic and amitotic divisions.

Group 2. Although many nongranular cells are present, most of them contain fairly large numbers of alpha granules. Some of the cells in this group show small vacuols in the cytoplasm, but the nuclei generally are reticular and appear to be fairly active.

Group 3. Here the alpha granules are very much smaller and appear only at the periphery of variable number of cells as a thin ring.

Group 4. No alpha granules are definitely demonstrated, but the periphery of some of the cells retain ethyl-violet stain quite definitely.

Group 5. The cells here are relatively inactive taking less stain;and the tumors are further characterized by increase of intercellular connective tissue and blood vessels. There are no alpha granules.

Group 6. Glandular cells are few and inactive. They show no sign of alpha granules. Active nuclei are not found, and the cytoplasm of the remaining cells has

a distinct tendency to vacuolization.

The cases which Bailey and Cushing[6] examined all appeared to have passed the peak of systemic hypertrophic changes. They fell into the above groups in the following proportions:

Groups 1 and 2 - eight cases each.

Groups 3 and 4 - eleven cases each.

Group 5 - forty seven cases

Group 6 - twelve cases.

Three of the cases had indefinite characteristics and could not be classified as above.

It was seen by correlation of the clinical aspects that the more marked acromegalic tendencies were in those patients who showed larger numbers of alpha granules in the cytoplasm of the tumor cells. These tumors were also definitely more cellular, the proportion of connective tissue and vascular stroma being greatly diminished. Cases operated after the onset of very distinct hypopituitary symptoms did not show this type of tumor. Some of these tumors showed cystic degeneration, actual vacuolation of the cellular elements, hemorrhage into the tumor or other destructive lesions. In the absence of these findings the tumors fell into groups 3 and 4, and in the later stages of hypopituitarism groups 5 and 6.

From these findings the authors arrive at the somewhat enthusiastic conclusion that the number of alpha granules and the acromegalic tendencies are proportional, and that the degree of hypopituitarism is proportional to the loss of these granules in the tumor cells.

These conclusions seem somewhat overdrawn but examination of other reported cases tends to confirm this impression. These findings seem further to confirm the impression that growth hormone is secreted by alpha cells.

Gross appearance of the tumors is variable. A large proportion of them are very small and can be found only after careful examination of the anterior lobe. These cases have no eye symptoms, marked headache or other pressure symptoms;and the other functions of the pituitary are, in general, well preserved. In contrast to these small tumors are the very large adenomatous growths which are generally considered as intrasellar or extrasellar tumors. The differenciation is made upon the presence or absence of extension beyond the fibrous diaphragm which separates the sella from the rest of the cranial cavity.

The intrasellar tumors may produce rather marked pressure signs and expecially those involving the optic

nerves. Associated with these tumors we may see very great enlargement of the sella, and the characteristic pituitary headache may be severe even in the absence of marked increase in intracranial pressure. The extrasellar tumors are those which have extended beyond the limits of the diaphragm. The extent of these tumors into brain tissue is variable but may involve large parts of brain tissue and may be associated with very great intracranial pressure. The focal symptoms depend upon the areas of the brain involved. Most of the tumors are fairly well encapsulated but some show erosion of the capsule with some of the invasive characteristics of malignant tumors.

Tumors examined late in the disease almost invariably show cellular changes with loss of granules and other signs of loss of secretory activity. These tumors are the type so well described in Cushing's studies. Associated are the late signs of pituitary deficiency. The pars intermedius and pars nervosa show more or less destruction by pressure from the tumor.

In considering acromegaly without definite tumor formation, we must recognize the fact that this is a very rare condition and that those cases where it has

been described are often indefinite acromegaly or the examination was not donvincing. Dean Lewis[46] reported such a case in which he described the microscopic picture as a very cellular gland with reduced stroma and cells resting directly on the capillary walls with irregular groupings. This is apparently the most authentic example of the condition. Krumbhaar[41] found a somewhat similar case. There was some increase in the size of the anterior lobe with an essentially diffuse cellular arrangement and definite increase in proportion of the alpha cells throughout the gland. Here we see a theoretical circumstance which seems to have pathological foundation in isolated cases but should be accepted after diagnosis has been proven and exhaustive searches for tumors completed.

THYROID

The response of the thyroid gland was subject of some controversy in the early study of acromegaly. In Marie's original case the gland was found to be rather small, weighing only 27 grams as compared to the average weight of about 45 grams. This, however, is not the common finding for thyroids in acromegaly though it was supported by other autopsy findings soon after Marie's time, as in Lewis'[46] work.

In general the larger percentage of cases seem to

have definitely enlarged thyroids during the active stages of acromegaly. The action of anterior growth hormone was studied experimentally by Paal[52] who, as we have seen, caused definite stimulation of growth of this tissue by addition of the growth hormone to cultures. He suggested the presence of a thyrotrophic factor which might be separated but this, if present, is also secreted by the alpha cells.

In cases which have progressed to the stage of decreased pituitary function, the thyroid gland is usually also small. In these instances the ascinal epithelium is relatively flat and an excess of colloid is present. Such a histological appearance seems to represent a diminution in function of the gland. We see here a series of events during which the thyroid hypertrophies from stimulation with the growth hormone to a plane at which it is impossible for the gland cells to continue their activity when the hormone is removed.

PARATHYROID

The literature contains relatively little as regards the changes in these glands and there is apparently very slight pathological or functional change. Cushing and Davidoff[19] mention Josefson's report of a case in which a tumor of the parathyroid "as big as a walnut" was found, but such instances are very rare

and may be accidental.

ADRENALS

Enlargement, which is characteristic of findings elsewhere in the body , is also found in the adrenal glands. Again, however, degenerative changes may be seen late in the disease. One of Cushing's[17] cases showed extreme fatty degeneration of the cortical cells which had previously showed marked hypertrophy to the extent of compression of the medulla which was very small. This seems to indicate a secondary regression of tissue following the removal of the growth hormone. Certain other cases treated at the Peter Bent Brigham hospital showed adenomatous proliferation of the cortex to be associated with the hyperplasia.

PANCREATIC ISLANDS

It is generally accepted that acromegalics have a tendency to hyperglycemia whether a glycosuria is seen or not. Cahne[*19] produced hyperclycemia by injections of emulsions of anterior pituitary and an accompanying decrease in muscle glycogen. There is also a tendency toward increase in number of islet cells in the pancreas. In some cases there is actual tumor formation in these cells (Cecil[11]) Whether the growth hormone is directly responsible for this or not may be questioned in view

of Cecil's suggestion that part of the hypertrophy at least may be a compensatory reaction to the tendency to increase blood sugar as mentioned above. If true, this could be considered a normal reaction corresponding to that which occurs in the foetus of a diabetic mother.

THYMUS

Grossly the thymus is always prominent. In some instances it is very much enlarged. This is not always associated with diffuse hyperplasia of the lymphatic tissues but the two are frequently seen together. Histologically there is nothing characteristic about the gland in acromegaly, but the enlargement is usually much greater than that of the other body organs.

GONADS

Two processes are involved in the pathological changes in the gonads. They are apparently affected very little by the growth hormone and, due to the frequent destruction or compression of the basophilic cells of the pituitary and resulting decrease in secretion of the sex hormone, there is a tendency to atrophic changes here. Cystic degeneration of the ovaries is frequently seen. In general the changes are those seen in hypopituitarism rather than a hyperfunctional syndrome.

In certain cases the sex factor is apparently not involved and its presence allows for continuation of

function of the ovaries. Teal[69] reports a case of an acromegalic who had symptoms for seven years with regular menses that showed no discernable change in character. At autopsy an eosinophilic adenoma was found but the basophilic cells seemed normal in appearance and number. Another similar case was reported by Bringle[8] in 1937 without autopsy findings where a patient showed symptoms for three years, was operated and an alpha cell tumor removed. Three years later she became pregnant and delivered a normal baby at term.

In acromegalics a marked hypertrophy of the genital tract is seen corresponding in general to the other visceral enlargement. Pathological changes of the ovaries seem more dependent on the sex hormone deficiency than increase in the growth factor.

Histological examination shows lack of signs of maturation and absence of lutein tissue. Testicular changes are rather similar to those seen in the ovaries. Spermatogenesis is not seen. The only remnants of the germ cells are small, inactive epithelial-like cells lining the tubules. Leydig and Sertoli cells have lost their histological characteristics and cannot be definitely recognized in sections of testes in advanced acromegalics. Crowe, Cushing and Homans[15] produced similar conditions in gonads of rats by hypophysectomy, confirming

the impression that the process here results from lack of the sex factor of pituitary secretion.

BONES

The bony framwork of acromegalics is probably the most described phase of the disease. The enlargements of skeletal structures made them the most obvious deformities and therefore were studied first.

There is, ofcourse, general enlargement with some lengthening of the bones and the height may increase from one to four inches. The bony changes may be summarized under five major processes, namely:

1. Thickening of the cortices of the long bones with enlargement of the bony processes such as muscle attachments, processes surrounding the joint contours and the irregularities of the flat bones accompanied by increased density.
2. Tufting of the terminal phalanges of the fingers in particular, a change which is practically pathonumonic of this disease and is not seen in other osteopathies.
3. Fusion of the epiphyseal lines occurring to the extent that they cannot be discerned either by X-ray or gross examination.
4. Exostoses appearing on almost any bony surface.

5. Lengthening, especially of the long bones. This is seen more particularly in young patients, becoming a less conspicuous factor as the disease occurs in later life.

These processes can be applied to account for all the changes in the skeletal size and contour in acromegaly.

VISCEROMEGALY

Visceromegaly as a separate pathological finding should be applied only to those cases where the viscera are enlarged out of all proportion to the general body enlargement. Atkinson[5] finds the condition to be relatively rare and it occured in only 46 cases in a series of 1400 which he reviewed. He pointed out, however, that it is not seen except in acromegalics and thus should be considered as one of the manifestations of the disease.

Sometimes the enlargement of internal organs is enormous as was found in a case of Roberts, Comb and Lond[58] where the stomach, intestine, colon, spleen and liver as well as the heart were involved.

Special consideration should be given to the heart since Mason[49] observed that heart failure was the cause of death of acromegalics excluding intracranial complications, diabetes mellitus, surgical procedures,

or other intervening disease. He found a marked cardiomegaly which is even more pronouced in those patients with remarkable enlargement of the viscera. One of the largest hearts on record was that of an acromegalic reported by Osborne[51], which weighed 1230 grams. The pathological process involved in these hearts is not well understood. It does not seem to be a matter of work hypertrophy. Sections show no characteristic changes. Early in the disease the muscle fibers seem to be larger than normal but later cases seem to show a decrease in size.

If we correlate the generalized atrophic changes which occur in the hypopituitary phaze with the cardiac decompensation seen here, it is conceivable that a heart which has been deprived of the stimulation of the growth hormone which has maintained the progressive hypertrophy should not be able to carry on adequate circulation in a vascular system adapted to the increased cardiac force. Rowe[57] finds that there is no marked increase in the blood pressure, but implies an increase in the vascular bed in the tissues. If this occurs simultaneously with the cardiac hypertrophy, the maintenance of the blood pressure will require sustained increase of work since the peripheral resistance is reduced with an accompanying increase in rate of flow and blood volume necessarily

	Height cm.	Weight kg.	Lungs gm.	Heart gm.	Liver gm.	Kidneys gm.	Spleen gm.	Thyroid gm.	Thymus gm.	Adrenals gm.	Pancreas gm.
Normal male	172	70	920	320	1500	300	200	45	14	12	80
Normal female	155	55		250							
Case I. male a. 52 dur. 30 Yrs.	185 6' 2"	97 213#	2550	1050	3150	853	535	310	?	43	225
Case II male a. 40 dur. 13 Yrs.	198 6' 6"	122.4 269#	1930	480	3380	565	385	105	8.2	43	83
Case III male a 35 dur. 20 Yrs.	173 5' 8"	100 220#	?	1000	2480	650	?	100	78	30	150
Case IV Fem. a. 51 dur. 21 Yrs.	157.5 5' 2"	68 151#	?	460	2500	695	240	?	?	18	?
Largest recorded weights	-	-	2922 (Osborne)	1275 "	5900 (Dallemagne)	1170	1169 (Lewis)	312 (Geddes)	Case III	57 (Schultze)	250 (Launois)

handled by the heart.

SOMATIC SOFT PARTS

This is evidenced chiefly by the increase in the size of the muscles. This, too, is a reversable reaction and degenerative changes occur in the late stages. Early, muscle fibers are large with distinct myofibrils; later, as the atrophic stage appears, they become shrunken in size with increase in proportion of connective tissue.

The chart on the following page is presented by Cushing and Davidoff[18] and gives some comparative weights and measurements of acromegalics.

TREATMENT

From our consideration of this disease syndrome so far we are made aware of certain distinct obstacles as regards the matter of treatment. In the first place, the pathological processes involved result in hypertrophy of the tissues of all of the organs of the body to a greater or lesser degree. This produces the characteristic deformities and makes return to normal relationships a destructive process, or at least, a shrinking of tissues and organs.

At the present time there is no known agent or program which can produce such changes. This being the case, we must content ourselves with stopping the progress of the symptoms and making the patient more comfortable if he is troubled with pain, loss of vision or other symptoms associated with the local effects of tumor growths as they may occur in the pituitary gland itself.

Effectively accomplishing this result is a very hazardous procedure because of the anatomical relationships of the pituitary gland and the technical difficulties involved in any therapeutic approach to it. Surgical removal is a very delicate matter technically and, if successful, the danger of pituitary insufficiency following is a very major one and should be done only with this

in mind. The relief , which can be expected, must be sufficient to warrent such a severe procedure. Perhaps in time our knowledge of the endocrine system in general will make it possible to simulate the function of the normal gland closely enough to make a fairly normal existance possible by administrations of certain extracts. As we see from the brief survey of the work done with the growth factor, much effort has been put forth toward this end, but the answer to the whole mechanism of pituitary function is something still to be desired. X-ray too has its limitations, chiefly in respect to selective, adequate exposure of the abnormal cells of the pituitary body. Endocrine therapy seems rather difficult to consider since the changes seen are due to an excess rather than a deficiency of hormone. In the absence of local symptoms, an agent which would result in the inactivation of the growth hormone, would theoretically be useful. Unfortunately no such substance has been discovered. Kirklin and Wilder's[39] suggestion of an antagonism of follicular hormone has the superficial appearance of a helpful measure, but their results are very questionable.

We shall consider treatment under three headings, namely irridation, surgery, and glandular.

IRRADIATION

Irradiation shall be construed to include both X-ray and radium therapy. First of all, the various tumors of the pituitary gland are distinctly different as to their sensitivity th these rays. Kerley[37] has studied this rather extensively and finds that acidophilic adenomata are very radiosensitive and respond almost immediately to treatment, but chromophobe adenomata are radio resistant and the growth of the tumor cannot be influenced by irradiation. Surface exposure to X-ray is occasionally adequate to stop growth of the pituitary tumor, but radium must be implanted within the gland if it is to be effective without over exposure of surrounding tissues. (Sargent and Cade[62])

Burlac*[17] was one of the first to use X-ray. He reported a patient who was relieved in two months of severe headache and the left field of vision was trippled in ten weeks by weekly radiation over the frontal temporal region. Webster and Teal*[17] also report favorable results from such treatment.

Radium rays are applied in two principle ways. In either method the tumor must be exposed surgically and the radio active substance placed within the gland. Platinum needles containing radium dust may be inserted or

radon seeds used in the same fashion. These seeds reach the maximum emmination immediately after implantation and the number of rays produced diminishes as they remain in the gland. Therefore the seeds may be left in place without danger of over exposure of tissue.

Lodge[47] described his work with this source of radiation. He pointed out two requirements essential to satisfactory results, intrasellar location of the tumor and lack of calcification. X-ray studies are essential and are usually sufficient to determine the extent of the tumor. Those cases in which the clinnoid processes are still intact and the base of the sella can be distinctly outlined may safely be considered intrasellar tumors. If spontaneous decompression has occurred as evidenced by erosion of the sellar base, implantation should not be considered. When the tumor has extended beyond the area of its fossa for a considerable distance, one cannot depend upon adequate radiation of the outlying portions. Excessive doses of radium result in permanent destruction of the optic nerve fibers and present the findings of optic atrophy.

Calcification of parts of the tumor sets up a shield which protects parts of the tumor from the rays. Lodge further developed a modification of Chiari's

operation for orbito-nasal approach to the pituitary fossa. He makes an incision vertically in the midline on the bridge of the nose and disects the medial orbital fascia away from the bone and retracts the contents of the orbit laterally with a specially devised "teaspoon" retractor. This also displaces the angular vein which is the only one causing trouble in hemostasis. He proceeds by chipping away the bone of the medial side of the orbit and upon reaching the base of the sella picks away the carapace of the adenoma which is usually delivered spontaneously at this stage by the intracranial pressure from above. The radon seeds are then inserted with an implanting needle. He considers three seeds an adequate dose.

Weakeley[72] reaches the gland by way of a transfrontal operation and implants nine radon seeds and does not report any indications of over radiation. He does not state the thickness of platinum shield used for the seeds.

Sargent and Cade[62] also showed that normal nervous tissue is resistant to gamma rays in therapeutic doses while the growth of tumors is inhibited. The necrosis which sometimes occurs in surrounding normal tissue is, in their opinion, due to the presence of beta rays unless excessive doses of gamma rays are

applied. Accordingly they emphasize the necessity of proper filtration of the radiation.

The conditions most advantageous are low linear intensity, pure gamma irradiation and a prolonged time factor. They found that radon seeds of either three or five mc. strength screened by 0.3 mm. of platinum or silver, caused necrosis of tissue of the vicinity immediatly surrounding the tumor. The same result followed the use of 10 mm. tubes of radium left in position for ten days. When radon seeds containing 1.2 mc. and screened by 0.5 mm. of platinum are used, very desirable effects are obtained. Two to three seeds were found to be an adequate dose.

They report one case in which ten such seeds were inserted into the sella of a patient with contracted visual fields and severe headaches. The headaches disappeared and the visual fields improved for a time after which optic atrophy supervened. Later operation showed necrosis of what appeared to have been normal gland tissue within the sella and a small area surrounding. Cases in which fewer seeds were used showed quite satisfactory results without the ensuing necrosis.

We may conclude from these findings that the effectiveness of irradiation applied to acidophilic

tumors depends upon the presence of a distinct increase in sensitivity of the tumor cells. Massive doses of radiation are unnecessary and only result in the complication of normal tissue destruction.

Frazier[26] used both X-ray and radium as routine post-operative treatment, but recognized the dangers of infection involved in any manipulations after the time of operation. He also showed, however, that X-ray radiation is more effective when administered either directly to the gland at time of operation or through that same surgical pathway later.

SURGERY

There has been a great deal of difference in opinion as to the place of surgery in treatment of acromegaly. Since the disease is one of glandular hyperactivity, removal of the gland responsible is obviously the direct method of removing the causitive agent. Thus, if we are to remove the cause we must consider the surgical extirpation of the anterior lobe of the gland or the tumor from which the growth hormone is being secreted in excess. Further than this, certain plastic and orthopedic operations may be considered in attempts to correct the deformities resulting from the hyperplastic processes so characteristic of this disease.

The first to be considered is the surgery involved in symptomatic relief. Cushing[17] treated a great many cases of acromegaly. He relieved nasal obstruction, which had resulted from thickening of the turbinates in particular and the general thickening of the bony plates surrounding the nose, by submucous resection.

The only other organ upon which it is necessary to do local surgery is the mouth. In this instance, glossomegaly and extention of the mandible result in difficulty in eating. To correct this the mandible is shortened by resection of portions of the ramus on either side and wiring of the fragments together. By this method it is possible to improve the bite thereby enabling the patient to chew his food. Weakeley[72] treated a case by this method and obtained a very satisfactory result. The same patient had a very large tongue. This was treated by a partial glossectomy.

Orthopedic treatment of the extremities has not been carried out since such surgery would involve extensive osteoplastic procedures which would effect a greater surgical shock than would be justified by the results anticipated.

The second type of surgical treatment is the attack upon the gland itself. This has but two possible indications. The first of these is the treat-

ment of tumors of the gland considering it as a brain tumor without regard for endocrine factor. The second indication would be an attempt to stop the progression of the endocrine symptoms when there are no particular local or focal signs of tumor. Most surgeons are of the opinion that the hazards of hypophysectomy are to great to justify it in simple glandular cases. They tend to reserve it for relief of intolerable headaches or failing vision.

There are two schools of thought regarding the approach to the gland. One group advocates the intradural approach and another group the extradural.

The chief method of extradural approach is the transphenoidal route. This was used by certain German surgeons as early as 1900 and was proposed in 1897 by Giordano. Cushing[17] gives a brief review of this work. Since the original work of Giordano is still untranslated, we quote from Cushing: "An operative approach with osteoplastic resection of the frontal sinus was proposed many years ago by Giordano, 1897. This was improved upon by Schloffer, 1906, who, by a transphenoidal and extracranial method, was the first to report a fairly successful operation. - - -

"Buccosphenoidal operations, similar to those used in animal experimentation, were proposed by Koenig,

1900, in which the superior maxillae were separated and the hard palate chiseled away. Loewe, 1905, suggested a similarly radical procedure with bilateral separation of the maxillae after deflecting the nose. These proposals of such severe and disfiguring operations are today interesting only from a retrospective point of view.

"With constant modification and progressive improvement the method of Giordano has been accepted and carried out by many. In Schloffer's first operation the nose was turned down to the right, and the turbinates, the mid septum, the wall of the orbit and maxillary sinus and the left nasal process of the superior maxilla together with the ethmoid cells, were excised - an exceptionally radical performance as can be judged. A similar but somewhat less extensive operation was employed by Hochenegg (cited by Stumme and Exner, 1909) with exenteration only of the septum and turbinates. "

Eiselberg's[17] adaptation of the method was likewise somewhat mutilating. He (cited by Cushing) used what he called a tunning fork incision and was able to make the approach by deflection of the nose to one side. Many other modifications of this procedure have been reported but they are all mutilating in their results to such an extent that they cannot be accepted for general use

even by members of the extradural school.

Chiari[12] made an approach by way of the orbito-nasal route in which he dissected along the medial wall of the orbit removing bone as he proceeded and retracting all the contents of the orbit laterally to allow for adequate exposure of the base of the sella. His incision was made beginning at the bridge of the nose and extending laterally and superiorly along the supraorbital ridge. The operation was originally designed for the removal of tumors but has since been adopted by Lodge[47] as a means of approach for the insertion of radium needles and radon seeds. Lodge[43] has further improved the operation, making it less disfiguring, by making his incision vertically in the mid line along the bridge of the nose. He also used this method to accomplish decompression of the sella, allowing the tumor to herniate through the sellar floor, thus relieving pressure upon the optic chiasm.

Cushing[17] has used a similar transphenoidal operation, but did not think it adequate to allow for surgical treatment of all types of tumors. He recognized its inadequacy in cases which much super-sellar extension as well as the difficulties encountered in aseptic technique while traversing such a notoriously contaminated structure as a paranasal sinus.

At first Frazier[27] was quite a devoute subscriber to this school of thought although he recognized certain limitations of any such operation. At this time ninty percent of the cases in which he considered surgical intervention necessary were patients whose chief complaint was loss of vision, and his primary objective was relief of pressure upon the optic tracts. That was accomplished by one of four procedures; sellar decompression, sellar decompression with excavation of the lesion, sellar decompression followed by X-ray or radium, or suprasellar subtotal extirpation.

For the first three of these he used the transphenoidal operation and for the last, the temporal approach. By 1928[28] he had practically abandoned the intranasal method in favor of the frontal. As early as 1921[27] he recognized the difficulty of attempting removal of the tumor by this route and at that time he used supplementary radiations when cases with marked tumor growth were operated by this method, either accidentally or by choice.

In 1923 Sargent[61] reviewed the situation regarding surgery of the pituitary as it existed at that time and arrived at some important conclusions. He considered surgery justifiable only in case of intolerable headaches or threatened blindness. He listed six fundamental

causes of failure in pituitary surgery as follows:

1. Errors of diagnosis.
2. Massive intracranial extension rendering the case unsuitable to any operation except a paliative decompression.
3. Operative accident.
4. Post-operative pituitary toxemia.
5. Post-operative pneumonia.
6. Septic infection in transphenoidal operations.

Two of these factors deserve special attention. The incidence of septic infection in transphenoidal operations was so high, compared with that in other methods of approach, that his work marked the beginning of a rather definite trend away from this treatment. Post-operative pituitary toxemia is a complication the cause of which is not yet well understood. It is a state of profound shock occurring one to four hours after operation and terminating fatally in spite of any supportive treatment which may be administered. It seems to be primarily a circulatory syndrome since the outstanding symptoms are progressively weakening pulse which soon assumes a thready character, cerebral anemia with loss of consciousness, and pallor. The loss of consciousness progresses to coma and death. Cardiac

stimulants have temporary effect which diminishes as doses are repeated.

Knaggs[40] believes the extradural operations to be indicated only under two conditions,

(a) when it can be rather certainly proven before operation that there is no intracranial extension which would prevent delivery of the tumor through subsellar decompression, and

(b) when there has been a spontaneous decompression resulting from erosion of the sellar floor.

He voices the present impression that in spite of the relative simplicity of technique of these operations, the danger of infection and possibility of failure to obtain adequate exposure makes it unwise to use this approach in practically 100% of cases.

As early as 1928, Frazier[28-29] abandoned extradural operations in the Pennsylvania Clinic, not only for technical reasons, but also because the cases so treated in that clinic showed a much higher incidence of recurrence than those treated by intradural operations.

In turning our attention now to the methods of intradural approach to the gland, we find two types, temporal and frontal. Horsley[35] was one of the first to attempt removal of the gland or its tumors by intradural approach. He divided his cases into two groups, one

to which he referred as true acromegaly, which presented symptoms of headache or loss of vision or both: and the second, the false acromegaly which presented only glandular symptoms. He considered surgery justified only in the true acromegalics, and believed the risk to be too great when the gland was not enlarged sufficiently to present the symptoms of loss of vision and headache. He devised an operation in which he turned down a large flap of the calavarium and exposed the gland by elevation of the temporal lobe of the brain. This was the temporal approach. There are important sinuses, vessels and nerves to be avoided but Knaggs[40] considers this approach preferable to the frontal route when the tumor occupies a position extending posteriorly from the sella.

Sargent[61] believes the temporal area decidedly more dangerous, even in the hands of competent surgeons, owing to the proximity of the retracted brain tissue to some of the vital centers of the cortex, especially the speech center. Other frequent complications are hemiplegias and ophthalmoplegias. He tends to favor a modification of Frazier's orbito-frontal operation. This was done by turning a flap of bone above the supra-orbital ridge, opening the dura and proceding posteriorly along the floor of the brain case. He removed part of the supra-orbital ridge, however, whereas Sargent turned a larger

flap superiorly and made resection of this ridge unnecessary.

Another feature of Frazier's[28] operation was the removal of the osseus roof of the sphenoid sinus to facilitate radium exposure by way of the nose postoperatively. He points out that even with the intradural method it is very often difficult to determine accurately the extent of the tumors and radiation should be added to the surgical treatment. Weakley[72] believes this method to be very advantageous and uses it for either extirpation of the gland or tumor, or as an approach for the implantation of radon seeds. This operation is somewhat similar to Lodge's modification of Chiari's orbito-frontal operation in which the dura is not opened.

Thus we see that surgery holds a very important place in the treatment of acromegaly. It must be used judiciously, however, after weighing carefully its expected achievements against the magnitude of the complaints at hand, keeping the grave dangers always in mind.

GLANDULAR

The place of glandular therapy is rather indefinitely established in the pituitary disorders. During

the active stage of acromegaly it seems apparent that the addition of pituitary extracts therapeutically would only increase the progression of symptoms (Knaggs[40]) Later in the disease, however, when signs of pituitary deficiency appear, these hormones would seem to have a place of definite value in the management of the disease. This has been found to be true by Teal[69], and Frazier[29] also found growth hormones of some value in preventing post-operative deficiency.

Kirklin and Wilder[39] administered the follicular hormone to eight proven cases of acromegaly and found what seemed to be a slowing of the hyperplastic processes. They used both theelin and amniotin. They suggested a possibility of some antagonistic or inhibitory actions but offer no physiological foundation for such activity. Further work may show these, or some related substance, to be of value but at present their use is only of experimental significance.

Following removal or destruction of parts of the gland with radium, the syndrome seen in fugitive acromegaly sometimes occurs. It is most commonly known as pituitary cachexia. Occasionally these same symptoms occur spontaneously as we have already seen in our examination of the progression of acromegaly as a disease.

In general the processes seen here are a reversal of those encountered in acromegaly. We see progressive and usually extreme emaciation, trophic changes of the skin, hair, nails, and teeth, evidence of general glandular hypofunction including a very low metabolic rate, amenorrhea and sterility in women, and impotence in men. (McCullagh[50]) The body temperature, blood sugar and blood pressure tend to be low. There is marked muscular weakness of the gastro-intestinal as well as the skeletal muscles. There may be a marked anemia associated and it is of interest to notice that diabetes insipidus is not a part of the picture. The syndrome similates Addison's disease without the pigmentation and it seems logical that some of these symptoms may be of adrenal origin in view of the fact that adrenal atrophy follows hypophysectomy in experimental animals.

McCullagh[50] finds that no treatment produces very satisfactory results. The administration of extracts of the anterior pituitary would seem to be the logical attack, but the scarcity of good results from such regime indicates this treatment is unsatisfactory at the present time. Even with the addition of pregnancy urine extract and thyroxin normal function cannot be restored. Adrenal cortical extract seems to be helpful in some cases.

It is evident that with our present inadequate knowledge and methods of preparation of the hormones of the pituitary gland for therapeutic purposes, adequate replacement therapy is impossible. It follows that treatment of pituitary cachexia is, at best, most unsatisfactory. The most that can be done with this type of replacement therapy is to make an early diagnosi of the condition and give the patient the advantage of available commercial preparations.

In 1937 Ehrhardt and Kittel[21] reported their results in the treatment of pituitary cachexia by means of transplants of pituitary gland, and at about the same time Kylin[42] reported twenty eight casses of Simmond's disease similarly treated. Ehrhardt[21] grafted pituitary tissue obtained from dogs into the abdominal wall just beneath the apponurosis of the recti or into the mesentary. The procedure is relatively simple if care is taken to prevent hemorrhage and subsequent clot formation around the grafts. Kylin[42] emphasized that the segment of gland implanted should be as small as possible and that fresh cut surfaces must be placed in close contact with the tissue to which the graft is applied.

This mode of treatment has the obvious advantage of offering all the hormones secreted by the gland, where as preparations of these hormones are not all

available for injection. The results were apparently very gratifying, but Ehrhardt and Kittel[21] found that a single graft was effective for only about one year. This method seems the most promising of any yet employed in replacing hormonal activity after hypophysectomy or other therapeutic or pathological destruction of the anterior pituitary.

CONCLUSIONS

After consideration of the material at hand we may formulate a definition of acromegaly. It is a metabolic disorder caused by an increase in the secretion of the pituitary growth hormone after normal growth is completed and is characterized principally by general body enlargement especially of the hands and feet the hands developing the characteristic "spade" form.

Further conclusions:

1. The disease is caused by an over-secretion of the normal growth hormone.

2. This hormone is secreted by the alpha cells of the anterior lobe of the pituitary.

3. The mechanism of action of the hormone is not well understood but it results in an increase in amount of body tissues.

4. Barring death in the early stages of the disease the hyperplastic processes are followed by signs of growth hormone deficiency and pituitary cachexia.

5. Other secretory activity of the gland tends to be decreased especially when there are definite

adenomata present.

6. Treatment is chiefly surgical or radiological, glandular therapy being very unsatisfactory.

7. After such treatment there tend to be signs of pituitary deficiency which must be dealt with by replacement therapy.

BIBLIOBRAPHY

1. Aldrich, T.B.
   On Feeding Young Pups the Anterior Lobe of the Pituitary.
   Am. J. Physiol, 30: 352-357, 1911-1912

2. Aldrich, T.B.
   On Feeding Young White Rats the Posterior and Anterior Parts of the Pituitary Body.
   Am. J. Physiol, 31: 94-101, 1912-13.

3. Allen, B.M.
   The Results of Extirpation of the Anterior Lobe of the Hypophysis and of the Thyroid of Rana pipiens Larvae.
   Science, 44: 755-757, 1916.

4. Allen, B.M.
   Experiments in the Transplantation of the Hypophysis of Adult Rana pipiens to Tadpoles.
   Science, 52: 274-276, 1920.

5. Atkinson, F.R.B.
   Study of the Literature on Acromegaly.
   Endocrinology 17: 308-320, 1936.

6. Bailey, P. and Cushing, H.
   The Microscopical Structure of the Adenomas in Acromegalic Dyspituitarism (Fugitive Acromegaly).
   Am. J. Path. 4: 545-561, 1928.

7. Bailey, P. and Davidoff, L.M.
   Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly.
   Am. J. Path. 1: 185-207, 1925.

8. Bringle, C.G.
   Pregnancy in an Acromegalic Following The Removal of Pituitary Tumor.
   Memphis M. J. 12: 72-73, May 1937.

9. Caldwell, C.T. and Rose, W.C.
   Feeding Experiments with mixtures of Highly Purified Amino Acids; Supplimenting Effect of Casein Fractions obtained by Carbamate Procedure.
   J. Biol. Chem 107: 45-55, Oct. 1934.

10. .....
Feeding Experiments with Mixtures of Highly Purified Amino Acids; Additional Properties of Unknown Growth Essential Present in Proteins.
J. Biol. Chem. 107: 57-73, Oct. 1934.

11. Cecil, R.L.
Concerning Adenomata Originating in the Islands of Langerhans.
J. Exper. Med. 13: 596-603, 1911.

12. Chiari, O.
Offizielles Protokall der Gesellschaft der Arzte in Wien.
Wien klin. Woch., 24: 955- , 1911.

13. Clark, L.N.
The Effect of Pituitary Substance on the Egg Production of the Domestic Fowl.
J. Biol. Chem. 22: 485, 1915.

14. Corey, E.L. and Graham, J.B.
Acromegaly Succeeded by Hypopituitarism.
Virginia Med. Monthly 58: 669-671, 1931-1932.

15. Crowe, S.J., Cushing, H. and Homans, J.
Experimental Hypophysectomy.
Bulletin of Johns Hopkins Hosp. 21: 127, 1910.

16. Cushing, H.W.
The Hypophysis Cerebri. (Address before A.M.A. 60th. Annual Session at Atlantic City - June 1909)
Jour. of the A.M.A. 53: 250-272, 1909.

17. Cushing, H.W.
The Pituitary Body and Its Disorders.
J.B.Lippincott Co.,
Philadelphia, 1912.

18. Cushing, H.W. and Davidoff, Leo M.
Monographs of the Rockefeller Institute for Medical Research.
1927.

19. Davidoff, L.M.
The Anamnesis and Symptomatology in 100 Cases of Acromegaly.
Endocrinology 10: 461-483, 1926.

20 .....
Studies in Acromegaly.
Endocrinology 10: 453-460, 1926

21. Ehrhardt, Karl, and Kittel, C.
Treatment of Pituitary Disorders by Grafting of the Pituitary Gland.
Ztschr. f. klin. Med. 132: 244-263, May 1937

22. Ellis, A.W.M.
Hyperglycemia in Acromegaly.
Lancet 206: 1200-1203, vi, 1924

23. Evans, H.M.
Glandular Physiology and Therapy.
Amer. Med. Assoc., Chicago, 1935.

24. Evans, H.M. and Long, J.A.
The Effect of Anterior Lobe Administered Intraperitoneally Upon Growth and Oestrus Cycles in Rats.
Anat. Rec. 21: 61-62, 1921

25. Evans, H.M., Meyer, K., Simpson,M.E. and Reichert,F.L.
Disturbances of Carbohydrate Metabolism in Normal Dog Injected with Pituitary Growth Hormone.
Proc. Soc. Exper. Biol. and Med. 29:857-861, 1932

26. Evans, H.M., Simpson,M.E. and Cornish,H.
Anterior Pituitary Extract Purified by Acetone Precipitation.
Proc. Soc. Exper. Biol. and Med. 27: 101-124, 1930

27. Frazier,
Contral of Pituitary Lesions Affecting Vision by Combined Surgical and X-ray-radium Treatment.
Arch. Ophthalmol. 50: 217-226, 1921

28. Frazier,
Surgery of the Pituitary Lesions.
Annals of Surg. 88: 1-5, 1928

29. Frazier,
A Series of Pituitary Pictures.
Arch. of Neurol. and Psychiat. 23: 656-695 1930.

30. Gaebler, O.H.
Some Effects of Anterior Pituitary Extracts on Nitrogen Metabolism, Water Balance and Energy Megabolism.
J. Exper. Med. 57: 349-363, 1933.

31. .....
Further Studies of Anterior Pituitary Extracts.
J. Biol. Chem. 100: xlvi-xlvii, May 1933.

32. .....
Effects of Thyro-parathyroidectomy and Carbohydrate Intake on the Action of Anterior Pituitary Extracts.
Am. J. Physiol. 110: 584-592, Jan. 1935.

33. Halliburton, W.D.
Handbook of Physiology. P. 343-345.
P. Blakiston's Son & Co.
Philadelphia 1913.

34. Hoskins, E.R. and Hoskins, M.M.
The Inter-relation of the Thyroid and Hypophysis in the Growth and Development of Frog Larvae.
Endocrinology 4: 1-32, 1920.

35. Horsley,
Diseases of the Pituitary Gland.
Brit. Med. Jour. v.1.: 323-338, Feb. 10, 1906.

36. Kerp, T.
Die Wirkung des Wachstumshormons der Hypophyse auf Erblich Zwergwuchs der Maus.
Klin. Wchnschr. 13: 1845-1846, Dec. 29, 1934.

37. Kerley,
Recent Advances in Radiology. p. 306.

38. Kingston H.L. and Schryver, S.B.
The Separation of Hydrolysis Products of Gelatin by the Carbomate Method.
Biochem Jour. 18: 1070-1078, 1924.

39. Kirklin, O.L. and Wilder, R.M.
Follicular Hormone Administered in Acromegaly.
Proc. Staff Meet. Mayo Clin. 11: 121-125, Feb. 19, 1936.

40. Knaggs, R.L.
Acromegaly.
The Brit. Jour. of Surg. 23: 69-82, 1935.

41. Krumbhaar, E.B.
Pituitary Disorders in their Relation to Acromegaly with Suggestions for the Use of More Precise Terminology.
M. Clin. N. Amer. 5: 927-956, 1921.

42. Kylin, Eskil
Hypophyseal Implantation.
Acta Med. Scandinav. 91: 428-434, Mar. 16, 1937.

43. Lackey, W.J.
Gigantism and Acromegaly.
South. Med. and Surg. Jour. 96: 275-277, June 1934.

44. Lee, M.O. and Schaffer, N.K.
Anterior Pituitary Growth Hormone and the Composition of Growth.
J. Nutrition 7: 337-363, 1932.

45. ..... , Teel, H.M. and Gagnon, J.
Basal Gaseous Metabolism of Giant Rats.
Proc. Soc. Exper. Biol. and Med. 27: 23-24, 1929.

46. Lewis, D.D.
Hyperplasia of the Chromophile Cells of the Hypophysis as the Cause of Acromegaly.
Bull. Johns Hopkins Hosp. 16: 157-164, 1905.

47. Lodge, W.O.
Treatment of Intrasellar Tumors by Radon.
Brit. Med. J. 2: 1257-1258, 1936.

48. Marie, Pierre
Essays on Acromegaly
The New Sydenham Society 1891

49. Mason, V. R.
The Heart in Acromegaly
Trans. of Assn. of Amer. Physician
51:220-229 May, 1936

50. McCullagh, E. P.
The Present Status of the Pituitary Gland and Clinical Medicine.
Ohio State Med. Jour. 33:379-384, April 1937

51. Osborne, O. T.
A Case of Acromegaly - Autopsy
Tr. Assn. Amer. Physicians. 12:262-277, 1897.

52. Paal, H.
Uber die Hormonale Bieinflussung des Stoffwechsels von Uberlebended Schildrussen Gewebe.
Arch. f. Exper. Path. 173: 513-525, Nov. 24, 1933.

53. Putnam, T. J., Teal, H. M. and Benedict, E. B.
Preparation of a Sterile Active Estrace of Anterior Lobe of Hypophysis.
Am. J. Physiol. 84:157-173, 1928

54. Putnam, T. J., Teal, H. M. and Benedict, E. B.
Studies in Acromegaly - Experimental Canine Aceomegaly Produced by the Injection of Anterior Bituitary Extract.
Arch. Surg. 18:1708-1731, 1929

55. Rake, B.
A Case of Acromegaly
Brit. Med. J. 1: 518-520, 1893

56. Reichert, R. L.
Effect of Anterior Pituitary Extract on Hypophysectomized Puppy.
Proc. Soc. Exper. Biol. and Med. 27:204-205, 1929

57. Rowe, A. W.
Energy Requirement of Acromegalic Giant.
Science 80: 482-483, Nov. 23, 1934

58. Roberts, F., Camb, M. D., and Lond M.R.C.P.
Acromegaly and Splanchnomegaly
Lancet 1: 25-26, Jan. 5, 1935

59. Robertson, T. B. and Burnett, T.C.
The Influence of the Anterior Lobe of the Pituitary Body Upon the Growth of Carcinoma Cells.
J. Exp. Med., 21: 280; 1915

60. Sandri, O.
Contribution a l'anatomie et 'a la Physiologie de l'hypophysie.
Archives italiennes de Biologie, 51:337-341, 1909

61. Sargent, Percy
Some Points in the Surgery of the Pituitary Gland.
Brit. Jour. of Surg. 11: 521-532, 1923

62. Sargent, P. and Cade, S.
The Treatment of Gliomata and Pituitary Tumors with Radium.
Brit. Jour. of Surg. 18: 501-520, 1930-31

63. Schafer, E. A.
Effects upon Growth and Metabolism of the Addition of Small Amounts of Ovarian Tissue, Pituitary, and Thyroid to the Normal Dietary of White Rats.
Quart. J. Exp. Physiol. 5: 203, 1912

64. Schitre, I.
Creatine-creatinine Metabolism in Acromegaly.
Quart. Jour. Med. 6: 17-33, 1937

65. Scott, T. B. and Broderick, F. W.
Therapeutic Uses of Anterior Pituitary Gland.
Practitioner 107: 278-287, Oct. 1921

66. Shelton, E. K., Cavanaugh, L.A. and Patak, P. R.
Acromegaly Followed by Pituitary Cachexia.
Endocrinology 20: 846-851, Nov. 1936

67. Smith, P. E.
Experimental Ablation of the Hypophysis in Frog Embryo.
Science, 49: 280-282, 1916

68. Smith, P. E.
Effect of Hypophysectomy in Early Embryo upon Growth and Development of Frog.
Anat. Rec. 11: 57-60, 1916-17

69. Teal, H. M.
Effect of Growth Principle of Hypophysis on Female Genital Tract.
Endocrinology 13:522-528, 1929

70. Teal, H. M. and Cushing, H.
Studies in Physiological Properties of Growth-promoting Extract of Anterior Hypophysis.
Endocrinology 14: 157-163, 1930

71. Uhlenhuth, E.
Experimental Production of a Giant by Feeding Anterior Pituitary.
J. General Physiol. 3: 347-365, Jan. 1921

72. Weakeley, C. P. G.
Case Treated with Radon Seeds: Partial Glossectomy and Bilateral Resection of Mandible.
Tr. M. Soc. London 59: 39-40, 1936

73. Windus, W., Catherwood, F.L., and Rose, W. C.
Feeding Experiments with Mixtures of Highly Purified Amino Acids - The supplementing Effects of the Casein Fractions.
J. Biol. Chem. 94: 173-184, 1931-32

74. Wulzen, Rosalind
The Pituitary Body. Its Effect on Growth and Fision of Planarian Worms.
J. Biol. Chem. 25: 625, 1916

* - Author mentioned in text cited from reference indicated.

###