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PITUITARY DWARFISM

BY

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INTRODUCTION

In the next few years Medicine will complete one of the great forward strides which have been typical of its progress through the ages. Hippocrates became the 'Father of Medicine' by virtue of his acute clinical observations and his accurate written descriptions. Galen incorporated the study of anatomy into medicine. Vesalius made that study a science. Leeuwenhoek, Spallanzani, Pasteur, Lister and others exposed the infectious nature of some diseases and forced medical thought to accept this fact. Von Baer discovered the mammalian ovum and modern embryology was born. Liebig introduced biochemistry. Claude Bernard laid the foundations for physiology. The virus as a source of disease was unveiled by the work of Beijerinck. In 1904 Bayliss and Starling defined internal secretion. Since then men like Cushing, Frohlich, Simmonds, Evans and Smith have pushed back the frontiers of our knowledge in regard to the mystical endocrine system until today we stand on the verge of a new and exciting field of medicine.

The tendency for each new discovery or theory to enjoy a rush of popularity followed by a pendulum swing to the opposite extreme, makes difficult the task of evaluating its use in medicine. It was this blind rush

that laid every ill of mankind, unexplainable by any existing knowledge, at the feet of Endocrinology. Many of these ailments have proved to be due to an imbalance of the glands of internal secretion. Indeed so large a number of bizzare and complicated derangements may exist that it would be impossible to deal with them all in a paper such as this. Even those due to the malfunctioning of one gland would make a lengthy subject. On the other hand it is impossible to separate completely one disorder from all others for, "The endocrine system", as Langdon-Brown says, "is an orchestra which must play in harmony and under the direction of its leader the pituitary".

Nevertheless the newness of the field and the apparent abundance of clinical material to be found on every side prompts one to write on some phase of this intriguing subject. The ideas and principles of today may be wrong tomorrow but the information obtained in working over the literature will provide a foundation for further study.

Pituitary dwarfism offers an opportunity to observe the methods of early investigations and to feel the stimulation of uncertain but partially successful results. The incidence of this disorder is high enough to justify

its study as an entity. Gordon reported in the Journal of the American Medical Association, in 1934, that forty-seven of one thousand children he studied exhibited retardation of growth attributable to anterior pituitary deficiency.

HISTORY

Dwarfs have been the objects of wonder, superstitious awe, ridicule and pity since earliest time. With the advance of knowledge in the fields of sociology, anatomy, physiology and internal medicine, the attitude has changed to one of scientific investigation.

The ancient Egyptians immortalized in stone the dwarf, Chnoum-hotep. The New Testament expresses the hopeless attitude of Biblical times toward the problem of growth in the statement, "Which of you by taking thought can add one cubit unto his stature?" The folklore of all European countries contains references to the 'little people'.

In 1864, the first suggestion that growth might in some way be controlled by an internal secretion was advanced by Verga. At that time there was no conception of endocrine glands or their secretions. Verga's statement was a shot in the dark and little or no attention was paid to the idea for several years. He based his proposition on his observation of a case of acromegaly with an abnormal pituitary body. (41) Pituitary dwarfism, described by Lorrain in 1871, was the first dwarfism to be described as a clinical entity. The cretinoid state, with its arresting physical signs, was the next

actual dwarfism to be described. The work was done by Gull in 1873, and it made such an impression on the minds of clinicians and surgeons that Kocher and Reverdin, in 1882, recognized and described the same condition following thyroidectomy. (21) This observation served to tie growth and glands together in the thought of scientists and to stimulate research along these lines. In 1887, Minkowsky revived Verga's idea that the pituitary played a part in the production of acromegaly, and in 1897, Massolongo went so far as to say that the syndrome was the result of hypersecretion by the hypophysis. This work was not on dwarfism but it afforded an opening wedge to the subject. (30) In 1908, Levi connected the state of underdevelopment described by Lorrain with pathology in the pituitary gland, starting a train of investigation which only recently has begun to turn up information of clinical value.

The period from 1900 to 1910 was rich with startling and contradictory observations by such men as Babinski, Frohlich and Cushing. They observed many cases of acromegaly with and without tumors and many cases of tumors without acromegaly. The fact was established by Cushing that the tumor responsible for acromegaly consisted predominately of acid staining cells, and from

this it was reasoned that a dearth of these cells might be responsible for under-growth. (6) The work of these men left little doubt that the pituitary gland was responsible for at least some aspects of growth. Bernard Aschner produced for the first time, in 1910, experimental dwarfism. Dogs were his subjects and his procedure was hypophysectomy. The lateral approach, thru a parietal bone flap and under the frontal lobes, produced a certain amount of brain trauma which might have been responsible for the arrest of growth. Subsequent work by Dandy and Reichert has eliminated brain trauma. They obtained ablation of the pituitary by an oral approach and produced results similar to Aschner's. (8)

Evans and Long, in 1921, administered an extract of the anterior lobe of the pituitary of oxen to rats. The extract was saline and was prepared by trituration of fresh gland and subsequent filtration. Thirty-eight animals were injected and a litter mate control was provided for each. The weight of the injected rats uniformly exceeded that of the controls. To remove objections to the work on the grounds that the experimental animals received extra nutrition from the injections, some of the controls were injected with fresh muscle extracts. These animals showed no greater growth than

the other controls. (15) This work proved that the hormone so vital to growth was elaborated in the anterior lobe.

In 1927, P. E. Smith performed hypophysectomy on rats and attempted to correct the resulting lesions by daily homotransplants. He reported, "Hypophysectomy produces an invariable and characteristic syndrome in the rat, chief features of which are inhibition of growth in the young animal, loss of weight in the mature, atrophy of thyroids, suprarenal cortex and sex organs, weakness and cachexia. The animal survives for months. The disability - - can be cured or nearly cured by daily pituitary homotransplants". This work demonstrates the production of a growth promoting substance by the pituitary. He also injected saline extracts, similar to those used by Evans and Long, and found that skeletal growth was stimulated but that the atrophied glands were not improved. (35)

In 1930, Smith wrote, "Hypophysectomized rats exhibit almost complete stoppage of skeletal growth - - immediately, showing that there is no storage of growth promoting hormone". (36) In the same paper, he agreed with other workers that posterior lobe destruction alone causes no cessation of growth.

The most recent experimental work was done by Dandy and Reichert in 1930. (8) They reported almost total cessation of skeletal growth in puppies. Their dogs continued to grow for one or two weeks before the arrest took place.

The experiments of these men supported by the work of others proves beyond reasonable doubt that there is a substance secreted by the anterior lobe of the hypophysis which is necessary for normal growth. It also proves that, in animals at least, replacement of this substance by extracts of the bovine anterior pituitary prevent the arrest of growth which follows removal of the hypophysis or its anterior lobe.

THE GROWTH HORMONE

Cushing says, "- - - should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, (in study of internal secretion), they were the discovery in the anterior lobe of the two separable hormones of growth and sex."

Herbert M. Evans' experimental studies (14, 15, 16) are largely responsible for the discovery of the growth hormone. Using rats his laboratory demonstrated the presence of a growth principle in the anterior hypophysis by chronic parenteral administration of anterior hypophyseal substance. Injection was started soon after weaning and gigantism resulted after some months of daily administration. After trying several preparations he finally settled on the following method of preparing an extract fairly rich in the growth stimulating factor:

"X grams of fresh bovine anterior lobe are ground in a mortar, with x/2 grams of clean sand, until reduced to a smooth paste. This mixture is weighed and 2 cc. of distilled water are added for every gram of ground glands. The volume of this mixture is measured and 3/8 its volume of .2N NaOH is added. As little as 15 minutes of extraction is adequate but the extraction can be allowed to

continue in the ice box 12 hours if more convenient. The alkaline extract is neutralized with .2N acetic acid, care being taken to stir constantly during the addition of the acid. An excess of acid is added so that the reaction of phenol red (1 drop of extract in 5 cc. water) is yellow. Alkali is then added cautiously until phenol red indicator shows the first pink tinge. The extract is centrifuged. The supernatant fluid is slightly cloudy and pale pink in color. This extract can be injected into rats without sterilization, but if desired, can be sterilized by passage through a Seitz filter." (14)

Smith repeated these experiments in the rat, using a similar extract, and supported Evans' results. (35)

In 1928, Evans and Simpson (16) reported that alkaline extracts stimulated growth in the adult rat at a level which never produced sexual maturity in the young and that acid extracts produce maturity in the young at levels which never produced growth in the adult. This indicated the presence of two distinct hormones and provided a method for their separation. They also called attention to the two cell types found in the anterior lobe, that is, the acidophile and the basophile.

It has been described elsewhere in this paper how

the acidophile cells were determined as the source of growth hormone. To repeat, the acidophile adenoma always accompanied those cases of giantism which reached autopsy.

In 1928, then, it was known that there was a substance in the anterior hypophysis which could be extracted with alkaline solutions and which when injected into laboratory animals produced increased growth. Commercial products purporting to contain this hormone began to appear on the market. Their use did not yield promising results. Cushing reported three cases of pituitary dwarfs treated with one commercial preparation without benefit. Later testing revealed that this extract was devoid of growth stimulating effect. (6) Putnam (24), working on experiments similar to Evans, was irked by the labor involved in preparing fresh extracts every day and cast about for a method of storing a large amount of extract for days at a time. In the course of search he found that heat, alcohol, phenol, mercurochrome, acriflavine and hexylresorcinol all either destroyed or precipitated the active principle. On this basis he stated that no product then on the market could possibly contain active growth principle. He devised a means of preparing a relatively sterile product

which could be stored under refrigeration for long periods. His method of extraction was similar to that of Evans. The anterior lobe of fresh beef pituitaries was shelled out after splitting the gland lengthwise. These were passed through a fine meat chopper and to every 100 gms. of pulp were added 5 gms. of Sodium Benzoate and 50 cc. of 1% NaOH. This mixture was made up to a liter with tap water and allowed to stand for several days in the cold. It is then passed through glass wool and neutralized with dilute HCl using phenol red as an indicator. A pH of 7.8 is the optimum. The extract is again allowed to stand for several days and is then doubly filtered, once through paper and again through a Sieck filter. It was stored aseptically. This is essentially the procedure used today.

Standardization of these extracts depends on the reaction of rats to their injection. The method advocated by Evans requires five or six animals, all female. Females are used because after about 150 days of life, a plateau in their growth is reached. After this plateau is established, rats on a standard diet gain at the rate of 10 gm. in twenty days. If these rats are injected with a potent extract they will gain about 50 or 55 gm. in total body weight in twenty days.

In this way products which are rich in growth producing hormone, those possessing some hormone, and those devoid of hormone, may be separated. (17)

By definition the growth principle described in the work of Evans, Smith, Putnam and others is a hormone for it is a chemical substance produced in one organ and carried by the blood to other organs, which it stimulated to activity. Abt prefers to call the principle a harmozone, a term which he reserved for substances which stimulate growth and development in contrast to those which promote immediate physiological activity. (1)

While many of the glandular preparations on the market today give promise, there are only a few of proven clinical value. The present status of the growth hormone is expressed by Shelton, "The present extracts are better than none but a more potent extract is needed." (28)

Anterior pituitary extract (Squibb) contains ten growth units per cc. and is marketed in 10 cc. rubber capped vials. It is standardized by injection into adult rats. One growth unit being the amount which will cause a weight gain of ten per cent in ten days.

Antuitrin-G (Parke, Davis & Company) has probably

been used more widely than any other product for experimentation. It contains ten growth units per cc. and is obtainable in 10 cc. vials. It is standardized by injection into adult rats. One unit is the amount which, injected intraperitoneally in two doses daily, will cause an average daily increase in body weight of one per cent per day for ten days.

Growth Complex (Armour) contains one hundred growth units per cc. It is standardized by the method of Collip, that is, hypophysectomized but otherwise untreated rats are used. One unit is that quantity, which, when administered daily in two divided doses over a period of ten or fifteen days by subcutaneous injections into rats weighing from eighty to one hundred grams, causes an increase in body weight of one gram per day.

The next step, and a big step in endocrinology it will be, is the isolation or synthesis of this hormone by the bio-chemists. In the meantime, it would be interesting to know whether the glands of young cattle in the growing stage would produce a more potent extract than that produced by extraction of all glands as received from the slaughter house, irrespective of the age of the donor. Shelton believes that the growth hormone is the same one that is involved in Simmonds' dis-

ease. If this is true, the age of the donor of the gland is of no consequence. Evans' work on standardization with adult rats and the fact of acromegaly suggest that the hormones are not the same.

PITUITARY DWARFISM

"Pituitary dwarfism is a chronic physiologic disorder having its origin in aberrant function of the pituitary gland during the period of somatic development and characterized by curtailment of the growth processes, with resultant small or diminutive stature and retention of other infantile characteristics." (31)

Dysfunction of the pituitary may be caused by one of several morbid processes. The dysfunction is of a particular portion of the gland, the acidophile cells. These may be compressed by tumors, removed by surgery, destroyed by infection or they may be congenitally absent.

Tumors which may compress the acidophile cells include the chromophobe adenoma of the pituitary and the embryonic rests known as craniopharyngioma.

Infarction, which is perhaps the greatest cause of acidophile hypofunction, is usually the result of embolism or of secondary involvement of the gland by a severe systemic disease in infancy.

Congenital absence of the cells does not appear to be common but it is the only way to account for those cases arising soon after birth without history of any disease or the demonstration of tumor.

Surgical ablation is rare and is usually the result of removal of pituitary adenomas.

The factors described above might be called the exciting etiology. In addition to these factors there appears to be in a few cases a hereditary tendency toward the disorder. Heredity, however, does not play a large part in the picture of pituitary dwarfism. There is apparently no age, sex, or environment which predisposes to the development of dwarfism.

The pathological picture produced by the chromophobe adenoma is one of compression. The acidophile cells are forced to the periphery and diminished in number. Instead of large cells containing a ring-shaped Golgi body and numerous large acid staining secretory granules, they appear as flattened atrophic cells. The tumor itself is made up of the small stain resisting cells. This tumor may be either intra or suprasellar. Ordinarily though it acts by compressing the secretory cells against the walls of the sella. It very seldom becomes malignant.

A similar picture is produced by the craniopharyngioma. This tumor is usually suprasellar and arises from the remnants of the primitive duct which extends from Rathke's pouch to the brain. It is more common

than the pituitary adenomas. Its structure is that of squamous or basal cell carcinoma. Its blood supply is poor and cystic degeneration usually occurs.

Infarction of the pituitary gland is the result of embolism or severe systemic disease. The incidence is unknown for it is thought to occur many times without diagnosis. The picture is one of lost cell detail and poor staining reaction. Part or all of the acidophile elements may be involved along with any or all of the other elements.

The most striking secondary pathology is in the long bones. The hypertrophy of the epiphyseal cartilage, which is the first step in the length-growth of these bones, does not occur. Consequently ossification seldom takes place at the proper time and the distinctive finding of open epiphyses long after the age of normal closing is characteristic.

Other secondary pathology includes cellular atrophy of other glands dependent upon the pituitary for stimulation. These glands include the adrenal cortex, the gonads and the thyroid. (43) Atrophic gonads indicate the involvement of the basophile cells of the pituitary.

The symptomatology of pituitary dwarfism is in-

fluenced by two factors, the extent to which the hypophysis is involved and the age of the victim at the time of onset. The majority of cases are marked by a sudden and complete cessation of growth. Erdheim has classified his cases by the time of onset as follows:

1. Nanosomia congenita - those cases in which there is no growth after birth. It is supposed that these cases represent a congenital absence of the acidophile cells of the pituitary. The intra-uterine growth is assured by the protective influence of the mother's hormones.
2. Nanosomia infantilis - cases whose onset occurs between birth and adolescence. These individuals grow normally until some pathological process, usually a systemic disease, involves the pituitary. They make up the majority of circus dwarfs. Tumors may be the etiological factor in these cases.
3. Nanosomia tarda - cases with onset occuring late in the growth period. These are the persons referred to as having 'stunted' growth. (3)

The subjective symptoms associated with hypopituitary dwarfism vary with the cause of the impaired pituitary function and with the extent of the impairment. Infarction of the pituitary gland as the result of severe systemic disease is apt to produce, besides dwarfism, a condition similar to Simmonds' disease. This is because the ischemic necrosis involves the entire anterior lobe in many instances. If this be the case, the patient suffers from marked cachexia, loss of sensation of hunger and thirst, and a feeling of depression.

Tumors of the pituitary gland itself seldom give rise to any of the symptoms of Simmonds' disease, but headaches are common and severe. Vomiting and vertigo complete the triad of symptoms common to increased intracranial pressure. These adenomas, if they escape from the confines of the sella, may also produce "neighborhood symptoms" such as primary optic atrophy due to direct pressure on the optic nerve. Boyd says in his Pathology of Internal Diseases, "The most characteristic pressure symptom is bitemporal homonymous hemianopia due to compression of the inner fibers of the optic chiasma on each side". The craniopharyngioma is more often guilty of these neighborhood symptoms than any other tumor.

Objective signs of pituitary infantilism provide the distinguishing features which were the stimulation to research. The outstanding sign is the arrested growth. The size of the afflicted individual, as already stated, depends on his age at the onset of the disorder. Boyd's picturesque description fits well, "The patient remains a graceful and attractive child, a Peter Pan who refuses to grow up". This physical make-up, a small but well-proportioned body is characteristic of the dwarf whose anterior pituitary is not completely destroyed. Complete destruction of the anterior lobe is accompanied by a wrinkled, atrophic skin and an oldish wizened expression - signs of Simmonds' disease. Fine, soft head hair and sparse or absent axillary and pubic hair are common. All of the organs including the teeth are proportionately small for the age. The dentition is usually poor and markedly retarded. The sexual apparatus in the majority of cases is undeveloped or atrophic. This is probably an indication of the involvement of the basophile cells by the primary pathology. The voice is high pitched and childlike. The intelligence is fairly normal in the typical case, but it may appear retarded as adolescence and adulthood approach in the absence of normal sexual

development. The appetite is small. (31)

There are dwarfs, apparently pituitary in type, who do not display the genital underdevelopment described above. It is thought by some that these individuals may represent an involvement of the acidophile cells alone. Such a condition is possible. The pathology involved would probably be a congenital absence of the acidophile cells.

Laboratory symptoms are few, emphasizing the physiological nature of this disorder. The blood picture is normal in the majority of cases but there may be a secondary anemia. The anemia is probably on the basis of a lowered iron intake due to the poor appetite. The urine presents no abnormal findings. The typical case is marked by a depressed basal metabolic rate, sometimes as low as -36. The blood pressure is characteristically low. Both the diastolic and systolic pressures are often below 100.

The x-ray findings in pituitary dwarfism are typical. The skeletal structure in general is slight. The bones are small but of normal structure in all respects except for the epiphyses. The epiphyseal line remains open much longer than in normal individuals. The epiphyses themselves are poorly outlined and contain mot-

tled rarified areas. This feature has been closely studied and bone age determination by x-ray of the hand has been worked out to a fine degree.

The diagnosis of pituitary dwarfism is difficult to make in the early stages of the disorder. The parents of the afflicted child seldom consider the arrested growth of any significance until it has been present for a rather long period. In fact, all the evidence indicates that the first stages of most cases are accompanied only by a slowing of the rate of growth and not by a complete and sudden cessation.

In suspected cases a thorough history must be taken. Among the points to be considered is the heredity of the individual, for there is indication that some cases are definitely familial. Previous illnesses of a severe systemic nature should be inquired into carefully. Scarlet fever, measles, tuberculosis and syphilis should be especially looked for. Certain symptoms which might be considered as evidence of a prodromal stage occur in about half of the cases. These include polyuria, listlessness, somnolence and headache. Visual disturbances are often the primary complaint in cases due to tumor. All of these symptoms must be sought for and if present, weighed carefully.

The rate of growth if it can be determined is of the utmost importance. School and home records may be called on to aid in establishing this factor.

Laboratory tests should of course include the basal metabolic rate, complete blood count, routine urine analysis and such blood chemistry as may be necessary to form a differential diagnosis.

Perhaps the most constant finding and, therefore, the most valuable one is the x-ray picture. This has been described under symptomatology.

Once the arrest of growth has been demonstrated and the diagnosis of pituitary dwarfism has been made, the untreated case follows a static course. Beumer (2) states that spontaneous sudden increases in growth seem to be the rule. This assertion is not borne out by case reports in the literature. According to these reports, the typical case never grows again without treatment. The individual progresses through puberty into adulthood and on through life shorter than his friends and acquaintances. The fundamental pathology in the pituitary body produces little evidence of its presence other than the dwarfism. The person afflicted with this malady seldom dies as a direct result of it. Systemic diseases and local infections are perhaps more severe in the dwarf

and death is usually the result of an incidental infection. Whether the endocrine system plays any part in the phenomenon of allergy is a moot question, however, it is true that many of the pituitary dwarfs are subject to one or more of the manifestations of this ailment. Asthma, eczema, and other irritating processes often add to the burden of the patient. There are a few cases which develop a severe cachexia, closely resembling Simmonds' disease, and die from old age at a comparatively early chronological age. In general, however, the course of the disease is limited to the growing period and the shortened individual which we see as an adult is the end result of this morbid process.

The complications which may arise in the case of pituitary dwarfism may be divided into two groups: the physical and the psychic. The physical have been listed under the course of the disease. Simmonds' disease with its remarkable cachexia may be a disease entity and the cause of the dwarfism. In some cases, however, the cachexia develops many years after the onset of the dwarfism. In these cases it appears to be a true complication. It is marked by early senescence, loss of hair, falling out of teeth and wrinkled toneless skin. The patient may become comatose and gradually fail until death occurs.

Concurrent infections find a fertile ground in the pituitary dwarf. There is apparently little bodily resistance and the patient may suffer from skin diseases or more severe systemic reactions. These often become overwhelming and carry the patient off. The lack of appetite may be responsible for vitamin deficiencies, secondary anemias and general malaise.

Perhaps of more importance to the dwarf than any of the physical ailments which may accompany his disorder, is the psychic trauma incidental to reaching partial maturity and seeing himself outstripped by his fellows in both size and accomplishments. The mentality as previously stated is not impaired, that is, the intelligence or learning ability is normal. The desire to learn is, however, considerable lessened in many instances. This is a completely understandable mental attitude. With the loss of companionship of individuals of his age, the patient loses also the stimulation to intellectual development. Puberty, of course, produces an almost intollerable situation in those dwarfs who do not suffer from complete atrophy of the sexual organs. The urge for the company of the opposite sex is only strengthened by the enforced abstinence brought about by the normal youngsters impatience with physical handicaps. That

the conflict thus produced within the dwarfed individual does not lead to schizophrenia is probably explained by the very fact of his smallness which provides an escape mechanism. Indeed one of the patient's most difficult problems is to resist the temptation to escape the ordinary problems of life by hiding behind this short stature.

The prognosis of pure pituitary dwarfism is good as far as life is concerned. The prognosis for further growth without treatment is very pessimistic. With treatment the outlook is somewhat brighter but at the present it must still be guarded. Those cases due to pituitary tumor or to craniopharyngioma carry a more guarded prognosis in regard to life. These individuals bear the added danger found in all intracranial tumors.

DIFFERENTIAL DIAGNOSIS

Arrested growth may be a symptom of such a wide variety of disorders that the differential diagnosis of pituitary dwarfism becomes a complex procedure. H. Gardiner-Hill (18) classifies dwarfism as follows:

A. Simple Dwarfism
    1. Simple hereditary dwarfism
    2. Simple dwarfism due to developmental skeletal disease
        a. Achondroplasia
        b. Osteogenesis imperfecta
    3. Simple dwarfism due to acquired skeletal disease
        a. Simple and late rickets
        b. Spinal caries and deformities due to other causes
    4. Hypergonadal dwarfism
B. Dwarfism and Infantilism
    1. Cachectic
    2. Cachectic associated with more specific changes at growth cartilages
        a. Congenital lues
        b. Scurvy
        c. Coeliac rickets

d. Renal dwarfism

3. Endocrine

a. Hypopituitary

b. Hypothyroidic

c. Hypogonadal

This classification implies several facts which are not entirely accepted, and is therefore, open to criticism. It nevertheless furnished a working outline for differential diagnosis. Dwarfism alone, in this classification, refers to skeletal arrest, while dwarfism with infantilism indicates a general arrest of development; that is, retention of infantile physical and psychological attributes in adults. In this matter Gardiner-Hill makes a distinction which is in variance with the definition of pituitary dwarfism as given in this paper.

Simple hereditary dwarfism is characterized by a family history of the disorder. It is not pathological because aside from the size there is no other sign of abnormality or disease. Puberty occurs at the normal age, and the sex function is normal. This condition may be confused with a pure acidophile cell absence. The latter condition, however, is usually congenital and growth does not occur after birth, while in the former, growth occurs for a number of years comparable to that

of normal individuals, but much more slowly. Examples of this type of dwarfism may be found in the African pygmie and the Norwegian Lapp.

Simple dwarfism due to developmental skeletal disease includes such entities as achondroplasia, chondro-osteo-dystrophy and osteogenesis imperfecta. The shortness of stature in these disorders is due to gross deformities of the bones which are evident to even casual inspection. Achondroplastic dwarfs are easily distinguishable from the graceful pituitary form. They are misshapen, ugly little creatures whose arms and legs are too short for the torso of almost normal size. Osteogenesis imperfecta is marked by actual shortening of long bones due to fractures. Both of these conditions are associated with normal mental and sexual development.

Simple dwarfism due to acquired skeletal disease does not offer a particularly difficult diagnostic problem. Simple and late rickets usually manifest other signs of vitamin deficiency. At least the dietary history is suggestive. The x-ray picture is the diagnostic sign which makes the differentiation from pituitary dwarfism. Here the epiphyses are found to be "dished". There is an abundance of osteoid tissue, but there has

been a failure of deposition of calcium and phosphorus salts. The impression received from the x-ray pictures is similar to that experienced when viewing an old tent stake.

Of similar pathological nature but involving the spine rather than the long bones, is the dwarfism due to such diseases as poliomyelitis. Collapse of vertebral bodies due to spinal caries causes a shortening of the trunk. The disease may be so severe as to cause an impairment of long bone growth, but the discrepancy between trunk and limb measurement is so obvious as to make differentiation a fairly simple procedure. Poliomyelitis is apt to produce a dwarfing of this nature due to the uneven tension on the vertebral bodies caused by weakening of one group of muscles.

Hypergonadal dwarfism is actually pituitary in nature. There is some question as to the cause of cessation of growth. It is possible that the mechanism involves a hyper-secretion of sex hormone which may be responsible for premature closing of the epiphyses. A more likely mechanism is a hypo-secretion of growth hormone without involvement of the sex hormone. The importance of differentiating this type of dwarfism from the classical pituitary type lies in the fact that the closed

epiphysis preclude the possibility of treatment with the growth hormone.

That group of dwarfism associated with retention of infantile sexual and mental processes is particularly difficult to differentiate. The cachectic dwarfism of the above classification is due to chronic wasting diseases during the growing period. Since pituitary pathology may result from such diseases the differentiation involves a nice judgement on the part of the clinician. The diseases involved may be the same in both cases but more often the cachectic type of dwarfism is due to gastro-intestinal derangement causing an impaired assimilation of nutrition. An important point of difference is the acute nature of the disease which is apt to cause infarction of the pituitary, as compared to the chronic tendency of the cachectic dwarfism. Pituitary dwarfism is relatively abrupt in onset, and growth more nearly ceases while in the cachectic variety the yearly increment may continue but at a rate much slower than normal.

More specific and therefore easier to diagnose are the cachectic dwarfisms characterized by changes at the epiphyses. These include congenital lues which is characterized by syphilitic osteochondritis. The x-ray picture reveals an epiphysis interspersed with punched-out

areas. Scurvy which is one of this group is usually accompanied by other signs of connective tissue pathology in addition to the irregular epiphyses. The lesion here is a hemorrhage from the capillary loops of the epiphyses with subsequent calcification which prevents normal length growth. The dietary history will often reveal a lack of vitamin D.

Coeliac rickets produces a picture very similar to pituitary dwarfism except that there are other signs of rickets, such as bowed legs, the rachitic rosary and so forth. The history will reveal a chronic anorexia and debility.

Renal rickets should not afford a difficult diagnosis. It is accompanied by the common signs of chronic nephritis. The blood chemistry is typical, that is, the high non-protein nitrogen interferes with normal calcium metabolism. Most of these patients die before puberty.

The last main group is that of endocrine dwarfisms. Under this group comes pituitary dwarfism already described in detail.

The hypothyroidic dwarf is the classical cretin. That statement makes the differential diagnosis for the cretin presents a characteristic picture. A dull apathetic facies, narrow low forehead, puffy eyelids, a flat

nose and a large protruding tongue from which saliva drips, provide a picture which it would be difficult to confuse with any other. In this connection it must be kept in mind that, due to the influence of the pituitary as a master gland, there may be signs of thyroid involvment in true pituitary dwarfism. The low basal metabolic rate, the fine hair and the dry skin are not necessarily evidence of hypothyroidism but they may be.

Engelbach, Schafer and Brosius (12) classify aneoplastic endocrine dwarfism as:

a. hypopituitary

b. hypopituitarothyroidic

c. hypothyropituitary

By this method they intend to indicate that there is on the one hand a primary anterior lobe with a secondary thyroid deficiency, and on the other hand a primary thyroid with a secondary anterior lobe deficiency.

The hypogonadal dwarfism of Gardiner-Hill is probably a pituitary dwarfism in which the basophile cells have become involved.

TREATMENT

The treatment of pituitary dwarfism, in order to be complete, must embrace several approaches. Therapy which will remove the primary etiology has no effect on the symptoms of the disorder, nor will purely symptomatic treatment remove the pathological process involved.

Treatment directed toward the etiology of the disorder is not always feasible. Infarction of the pituitary, for instance, is as final and irreversible a step as is infarction of heart muscle. No method of supplementing the blood supply is practical. On the other hand tumors of the pituitary itself and of the rudimentary stalk to the brain may be attacked surgically. This is a very radical procedure and is most frequently used when the sight is threatened by encroachment upon the optic chiasma by tumor. Cushing (6) expressed the difficulty of the operation in the following statement: "No moonshiner, with every effort to throw searchers off the track ever secreted the spot where his demoralizing product was being distilled and prepared for distribution more skillfully than did Nature - -". He had reference to the pituitary body, although he was discussing a disease other than dwarfism. Both special knowledge and skill are needed to surgically remove

these tumors. Such cases become the responsibility of specialists. In the paper quoted above Cushing also reports the use of x-ray therapy in cases of pituitary adenoma. The ray stops further growth and even destroys some of the already present cells. It is not infallible but it does richly deserve a trial before the more radical surgical procedure is used. Radiation requires technical skill and is as specialized as surgery so that the counsel of a qualified radiologist should be sought. In the treatment multiple ports are used and the dosage is varied with the individual.

Treatment directed toward the pathology is achieved when the etiology is treated. The compressed acidophile cells are relieved when adenomata and craniopharyngioma are removed and the function of these cells may then be resumed. No treatment will remove the pathology of congenitally absent cells, nor will the infarcted gland be improved by treatment.

Secondary pathology as described previously, involves the long bones and the adrenal, gonads and the thyroid glands. Administration of the sex hormone in some form such as antuitrin-S, appears to stimulate the atrophied gonads to development. The thyroid gland and the adrenals are usually stimulated to development by

contaminates of the growth producing extracts. These impurities are apparently thyreotropic and adrenotropic factors of the anterior hypophysis. The extract used by P. E. Smith (35) did not repair the atrophied thyroid. Evans (14) attempted to completely separate these various factors. With the evidence of polyglandular involvement seen in the clinical case it does not seem desirable to use a too thoroughly purified extract. Care must be exercised, however, not to cause closure of the epiphyses before the desired growth has been obtained. Premature closure has taken place in children being treated with sex hormone.

Repair of the long bone pathology is accomplished by administration of the growth hormone. The point of action of the hormone is not known. As stated above it or its contaminates act on the several endocrine glands. Whether it is the result of this action or a separate and distinct effect on the osteoblasts, length-growth of the long bones is resumed in a fair percentage of the cases treated. In those cases which demonstrate a thyroid deficiency there is a correction of a calcification abnormality. This abnormality is described as multiple irregular islets of ossification in the cartilage. (42)

The symptoms of pituitary dwarfism are the primary subject of treatment in most cases. The primary symptom is the lack of growth. Directed toward the alleviation of this symptom is the administration of growth hormone. As stated in the chapter on this hormone it is still in the experimental stage. The dosage and the frequency of administration remain a matter of individual discretion. The literature well illustrates the undecided state of affairs in regard to this hormone, but it does provide a basis for estimating the optimal dosage of the hormone. A brief survey of the literature will serve to indicate the trend of clinical thought.

Engelbach (11), in 1932, reported what he believed to be the first human being treated with the anterior pituitary extract. His subject was a female child who had not grown since the age of three. At the time treatment was begun the child was nine and a half years of age. After testing the patient for sensitivity to the extract by small subcutaneous doses, he began treatment by injecting one cc. three times per week intramuscularly. This dose was gradually increased until it reached nine cc. six days per week. Treatment was continued for nine months and seventeen days. The child grew nearly three inches in this time and she showed greater interest in

her surroundings, appearing to be a much brighter individual.

In 1933, Engelbach and his associates (12) again reported on growth hormone therapy. Seven cases were followed. All showed favorable results. All cases were studied for a variable length of time prior to treatment as a means of assuring that any increment obtained was due to the medication. The initial dosage was one half cc. subcutaneously three to five times per week. This served to eliminate any risk of sensitivity. None of the patients showed any signs of sensitivity to the preparation. The dosage was increased to five cc. three to five times weekly. Any experimental value of this work was impaired if not completely obviated by the use of dessicated thyroid in some of the cases as supplemental therapy.

Cushing (6) reported in 1933 that he had treated three pituitary dwarfs, ranging in age from nineteen to thirty years, with antuitrin-G (Parke, Davis & Company anterior pituitary extract) in 1929. These cases received no benefit in regard to growth rate. Later testing revealed that the extract had lost its growth stimulating effect. Another batch of the same preparation produced one and a half inches growth in a seventeen year

old girl who had been three feet eleven and a half inches tall for many years. The injections of antuitrin-G began with two cc. intramuscularly and continued for 110 days gradually increasing to five cc. These were given three times a week.

Shelton, Cavanaugh and Evans (32) reported six cases in 1934. They reached these conclusions: 1.Growth is stimulated by intragluteal injection of extract of anterior hypophysis; 2.There is an improvement in facial expression and body development; 3.In its present form the extract is not satisfactory; 4.But, it is of value in cases of mildly arrested development.

The same year, Turner (40) reported several cases. His results ranged from no increment to a three and one half inch increase in height. The patient showing no improvement received five cc. of antuitrin-G intramuscularly daily, while the patient who gained three plus inches received only three cc. daily. The treatment extended over a thirteen month period. Turner offered no explanation of the difference in results but it is reasonable to assume that either the epiphyses of the first patient were closed or else the diagnosis may have been wrong. One of his cases received thyroid extract in addition to the pituitary extract. This

patient added six and two-tenths inches to his height.

In a follow-up report on their seven cases Engelbach and Schaefer (13) noted that four of the cases had increments varying from three and one-third to six inches. There had been noted a definite delay in osseous development in the preliminary study of these cases. Two of the original seven cases had been dropped because of the lack of response. They concluded this paper with the statement that sexual maturity was an unfavorable sign while immature osseous development was a favorable one in the prognosis of growth.

Shelton (31) in 1936 reported on one case. A twenty-seven year old dwarf grew one and seven tenths inches under treatment with anterior pituitary extract. The author stated that the present extracts would not rehabilitate the classic dwarf after maturity had been reached.

Eleven cases ranging from three to eighteen years of age were treated by Schaefer (27) in 1936. Increase in height varied from one and nine-tenths inches in a patient treated eleven months, to nine inches in a patient treated thirty-three months. He demonstrated that the gain in his patients was above that of normal individuals of the same age.

Sexton and Neuhoff (29) treated a diabetic pituitary dwarf with dessicated gland orally without result. Cattle transplants were then tried. The patient grew one and one half inches in less than a year. Treatment was stopped because the patient refused to cooperate.

In 1938, Lawrence and Harrison (23) treated a school boy of sixteen years with both antuitrin-S and antuitrin-G. They used two cc. of each three times weekly. There was a gain of six and one half inches in three years.

That same year, Sexton (28) reported on eight cases, five of whom added from one half to one inch to their heights in seven months. His hormone preparation was not designated.

Bronstein (4) reported one case in 1940. Moderate success was achieved with a commercially prepared extract.

Yarvis (44) reported on a thirteen year old boy who was forty six and three quarters inches tall at the beginning of treatment. He received antuitrin-G, 2 cc. three times a week and dessicated thyroid, grains one-quarter daily. The patient grew six and one half inches in fourteen months.

These papers indicate that the treatment of pituitary dwarfism should begin early and should be long

continued. The extracts used depend somewhat upon the individual. The commercial preparations of anterior hypophyseal which are available have been described in regard to standardization under the heading Growth Hormone. The recommended dosage and mode of treatment varies with the product. (3a)

The Squibb Company recommend that their product be administered intramuscularly in doses of .5 to 5 cc. three times a week. This is approximately equal to fifteen to one hundred and fifty growth units per week.

Parke, Davis & Company advise the use of six to ten cc. per week in doses of two to five cc., that is, sixty to one hundred growth units. The intramuscular route is recommended.

Armour's product contains one hundred growth units per cc. They recommend one or two cc. daily until sixty cc. have been given, then a rest period of thirty days. The rest period is to avoid building a resistance to the preparation. This product is to be used intramuscularly only.

There is no evidence in the literature to indicate that oral administration of any of these products, or of any other product, will produce growth. In fact all of the evidence appears to prove that oral administration

is a waste of time and money.

Dessicated thyroid given to tolerance is indicated in almost every case. Those cases which Evans would classify as hypothyropituitary, and in which the thyroid deficiency is so prominent as to raise the question of cretinism, respond especially well to this medication. This fact strengthens the position of those men who claim that there is no such thing as a uniglandular imbalance. Wilkins (42) described what he called 'epiphyseal dysgenesis' in pituitary dwarfism. Under treatment with thyroid substance the affected centers proceeded to ossify normally.

General supportive care plays an important part in the treatment of this disorder. Regular hours, a high caloric diet, and plenty of sleep must be provided. All of the vitamins must be present in sufficient amounts. Vitamins B, C and D especially play a major role in growth and development.

Dangers of therapy are few. It is possible, however, that prolonged and intensive therapy after the epiphyses have closed may produce acromegalic features. Interruption of the normal menstrual cycle has been known to occur, and a potent male patient has lost all libido under this treatment. Collip warns against the formation

of antihormones. Whether or not there is such a structure produced in the human body is still a question, but it is well to proceed as if this were an established fact for the time being. Perhaps the best method of preventing this catastrophe is to use the rest periods advised by Armour and Company in their literature.

CONCLUSION

Endocrinology constitutes a new and enlarging field of research and clinical interest. There is an almost unlimited number of clinical manifestations of the imbalance of one or more of the glands of internal secretion. Of this group we have discussed but one, pituitary dwarfism. As in all other endocrine disorders, there is much yet to be learned.

The identification of the growth hormone and of its mode of action are the important steps which remain to be taken in the study of this abnormality. Upon these facts will rest the ultimate treatment of this dwarfism. As now known, the hormone is an alkaline extract of the anterior hypophysis. Its action appears to be either a direct stimulation of the epiphyseal cartilage or an indirect one through the thyroid, the adrenals and the gonads.

Pituitary dwarfism itself is a classical picture. Early diagnosis is at times difficult due to the confusing symptoms introduced by the involvement of other endocrine glands. The untreated case presents a severe complication in the form of psychic trauma. The course is a static one if treatment is not instituted. The

prognosis for life is good but for growth in the untreated case it is poor.

Treatment consists of intramuscular injection of extracts of the anterior hypophysis. The dosage varies from two to seven cc. per week depending upon the extract used. General supportive care is important. The treatment should be instituted early and should continue for years in cases which are showing results.

The above information is taken from the literature which has, on the whole, an optimistic note. Results have not been uniformly good but success has been attained often enough to indicate that there is definite hope for the individual dwarfed by the impairment of pituitary function.

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