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ORAL MANIFESTATIONS OF ENDOCRINOPATHY

AND

ENDOCRINE THERAPY IN DENTISTRY

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INTRODUCTION.

The endocrine glands produce internal secretions called hormones, which act as stimulators or inhibitors of growth and body functions.

This principle of hormonal regulation of body functions was introduced to physiology relatively recently, during the nineteenth century and particularly so during the present century. But it really waited till very recent times for the functions of the endocrine glands to be elucidated. Tremendous advances in the field of endocrinology, which has become an important branch of Medicine, and has occurred in the past twenty years, following discovery and isolation of several of the important hormones. The isolation of pure parathyroid hormone, as recent as 1960 is an example of special interest. The extent of endocrinology is becoming increasingly broad, and the interrelationships of the endocrine glands becoming more understood. Yet, there is still a very great deal unknown as to the complex chemical structures and the physiology of the hormones.

Unlike nervous regulation that of the hormones is generalised, because of their discharge into the blood stream directly, from which they are distributed throughout the body. No tissue in the human body is exempt from some sort of hormonal influence, either in its course of development or in its functioning. The hormones, of which over 50 are known related to the mammalian body, vary much in chemical form and activity. They affect most body processes such as;

Growth-by the anterior lobe of the Pituitary gland and the Thyroid gland,

Metabolism-by the thyroid gland,

Calcium metabolism-by the parathyroid glands,

Carbohydrate metabolism-by the Islets of Langerhans particularly, but also by the adrenal cortex and anterior pituitary.

Sexual development and function-by the genital glands (gonads) through the anterior pituitary. The adrenal cortex is also involved.

Blood pressure-by the adrenal glands to some extent.

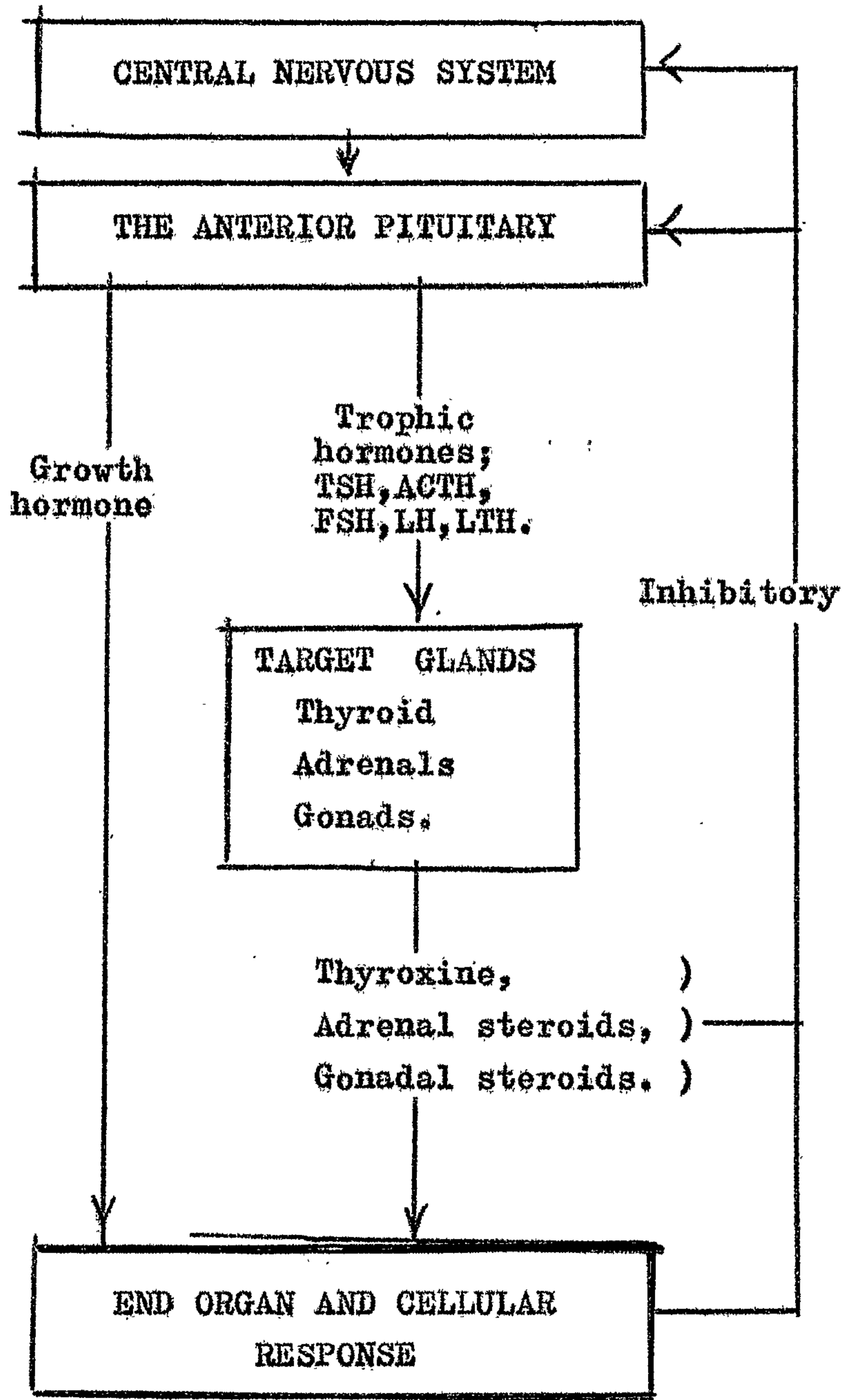
However, with few exceptions, hormones are not essential for life. In the rat for instance, neither thyroidectomy, gonadectomy nor hypophysectomy is fatal. Nevertheless after such operations many body processes are diminished and cannot be speeded up when the need arises. Physical and mental activity can be considerably impaired due to the consequent hormonal imbalance. The adrenal cortex is essential for life, replacement therapy being needed, if it is removed or diseased.

Much research has been undergone in the field of endocrinology especially on the effects of hormone administration and of endocrine gland removal on animals. The rat, mouse, dog, monkey, hamster, etc. have all been used in these experiments and have added much to our understanding of the hormones and their function, pathology, and relation to the oral structures.

The interrelationships of the endocrine glands are becoming increasingly understood, and are of importance in the understanding of endocrinopathy. The anterior pituitary, which has been described as "the master gland of the body" by its various hormones, is one such example. The endocrine system is related to the central nervous system, and also to external stress. (See diagram)

The profound effects on metabolism and growth of endocrine dysfunction have led at times, particularly in the past, to the error of regarding the endocrines as responsible for many conditions, the source of which cannot at present be proved. This applies to the oral region particularly.

In disorder of the endocrine glands there may be either hypersecretion or hyposecretion of hormones, and disorder of one gland often affects another gland, with consequent changes in many parts of the body. Such syndrome complexes are common in endocrinopathy.



Interrelationship of the endocrine glands, affecting growth and development. ( From Crigler, Cohen, and Wittenberg, 1962.)

As to the bearing of endocrinopathy on oral conditions, the remarks of Professor A.J. Arnott (1962) would serve as an excellent introduction.

"In order to develop satisfactory treatment plans for diseases of the oral cavity, it is necessary to accept that the oral tissues serve as sensitive indicators for many nutritional and metabolic disorders.

The oral tissues obey the same fundamental laws and exhibit the same basic phenomena as do other parts of the body. It is true that the oral structures are more readily observed and accessible, being close to the body's exterior.

There is much evidence to show that oral diseases frequently are in part or entirely manifestations of systemic diseases.

For example nutritional deficiency, blood dyscrasias, endocrine dysfunction, and infectious diseases produce many oral manifestations and dental caries, gingivitis, stomatitis, glossitis, hyperkeratosis, are just few of the diseases of the teeth and their supporting structures which are related to systemic deficiency and disease.

It is true that the oral tissues serve as sensitive indicators for many disorders of the body.

Incorporated in this critical review of the literature is the effect of endocrine dysfunction on cranio-facial development, the relationship of the jaws, dental development, condition of the supporting structures of the teeth, the oral mucosa, salivary glands and other related parts of the region. An introduction is given at the commencement of the consideration of each endocrine gland, in which its history, anatomy, histology, physiology, and interrelationships with other glands are briefly discussed. Also the pathology, histopathology and blood chemistry as affecting the body generally is referred to and the various disease syndromes described, before the oral manifestations are considered. Treatment and prognosis of the endocrinopathies is discussed also at the end of each section.

Experimental work on animals is fully dealt with on each gland. A section on the Salivary glands, Endocrine therapy in dentistry and also several syndromes simulating or related to endocrinopathies is also included at the end, together with a concluding summary of the oral manifestations.

This thesis, may serve to correct many incorrect statements made

made in the past and which are still current, and to gather together the available data as to oral conditions associated with hormonal dysfunction in the light of rapidly increased present-day advances in this important field.

THE PITUITARY GLAND  
(Hypophysis cerebri)

INTRODUCTORY.

The Pituitary gland has been described as "master gland of the body", Collip (1938). Cushing (1912) described its function stating "Here in this well concealed spot almost to be covered by a thumbnail, lies the very mainspring of primitive, vegetative, emotional and reproductive activity". These comments were made due to the fact that the Pituitary gland has an important trophic effect on other glands of the endocrine system.

It is composed of;

- 1) Anterior lobe (pars anterior, pars glandularis anterior hypophysis)
- 2) Posterior lobe (pars posterior, pars nervosa ) or posterior hypophysis, 20%.
- 3) Intermediate lobe (pars intermedia) and
- 4) Pars tuberalis makes up remaining 10%.

The intermediate lobe and pars tuberosa are rudimentary in man and probably of little significance, Hawker (1950). Ham (1953) indicates that the Intermediate lobe is developed in some animals and produces a hormone called "intermedia", described by Zondek and Krohn (1932) having specific pigmentation reactions but that both the Intermediate zone and pars tuberalis have an unknown function in man. This melanin-stimulating fraction of the intermediate lobe in animals has been called M.S.H.

The pituitary gland is an ectodermal derivative about 14x9x6 mms in size and weighing  $\frac{1}{2}$ gm, Cunningham (1947), and housed within the protecting sella turcica in the centre of the base of the skull. An interesting embryonic fact is that the anterior lobe, like the teeth is derived from the oral ectoderm (Rathke's Pouch, a diverticulum of the oral pituitary). This common derivation explains the occasional presence of teeth in pituitary tumours, Schurman, Pfluger and Norrenbock, (1931). The posterior lobe is derived from the diverticulum of the floor of the diencephalon, hence has a neural origin.

## Anterior Lobe and its Hormones.

It is generally agreed today that the anterior pituitary produces six definite hormones:

1. Growth Hormone - or somatotrophic hormone (STH)
2. Thyrotrophic hormone (TTH)
3. Adrenocorticotrophic hormone (ACTH)
4. Follicle stimulating hormone (FSH) a Gonadotrophic hormone
5. Luteinizing hormone (LH), a Gonadotrophic hormone (GTH)
6. Luteotrophic or lactogenic hormone (LTH)

Other hormones have been suspected, such as a metabolic hormone affecting carbohydrate, protein and fat metabolism, but whether it is a specific hormone or associated with STH, ACTH or other known hormones is unknown. A parathyrotrophic hormone has also been suspected but is doubtful.

The microscopic structure of the anterior pituitary is composed of gland cells in thick and irregular cords supported by reticuloendothelial fibres. Ham (1953) has described the following cells;

1. Chromophobe; Tumours of such have no effect on persons so they probably produce no hormone.
2. Chromophils; of which 75% are acidophils or eosinophils, tumours of which cause acromegaly and gigantism therefore apparently producing the Growth hormone; and 25% are basophils. Halmi (1950) and Purves and Griesbach showed beta and delta basophils, the former producing TTH and the latter LH. It is felt that the LTH comes from the acidophil cells, but it is not known yet from where ACTH comes.

The Growth Hormone. (STH), was discovered by Evans and Long (1921)

It governs particularly the growth of the skeleton. Consistent results were secured by the injection of anterior pituitary extract into normal animals and it was found effective in restoring dwarfed rats due to hypophysectomy. Growth stimulation has also been proved in human endocrine dwarfs when instituted before the puberal growth-spurt period. Englebach and Schaefer (1934), in the sense that it increases body size but apparently does not influence differentiation of body tissue in general since proliferation of cells and growth of individual organs and tissues continue in the absence of the anterior pituitary.

Best and Taylor (1961), state that "the anterior pituitary" appears to preside over the growth of the body as a whole and to control the proportional growth of the several organs and parts. Freud et al were led to believe that STH acts specifically on the proliferating zone of cartilage (1929) and also had a systemic effect, (1939). It is claimed that GTH is antagonistic to STH, and this was particularly shown in connection with the male sex hormones inhibiting growth of the epiphyseal cartilage and suppressing the elaboration of STH, Reiss et al (1946).

The Thyrotrophic hormone. (TTH) was demonstrated by Smith, (1927) in mammals. Loeb (1929) and Aron (1929) showed independently that injection of anterior pituitary extract into guinea pigs produced thyroid hyperplasia resembling the histological picture of Grave's Disease. It has been demonstrated that TTH in blood is increased in acromegaly and diminished in Simond's Disease. Radioactive iodine studies by Morton et al (1940) have shown that TTH especially controls the rate of iodine uptake by the thyroid and the conversion into thyroxine. Billingsley (1937) has presented evidence that TTH exerts a dual action on the Thyroid, firstly by influencing thyroxine production and discharge and secondly by producing changes in the gland morphology.

Adrenocorticotrophic Hormone (ACTH): Smith et al (1930) and Evans (1932) showed that following hypophysectomy, degenerative changes occurred in the adrenal cortex of the rat, and Loesser (1933) made similar observations. In the intact animal anterior lobe extract produces hypertrophy and the adrenal cortex, Putnam et al (1929)

The Gonadotrophic Hormones (GTH). It was discovered in (1927) by Smith and Engel and Smith (1935) described two hormones involved which have been investigated by Fevoid et al (1931) and (1940) in an extended series of experiments and Evans et al (1939). Li et al isolated one of these, the follicular stimulating hormone (FSH), and Claesson et al (1948) prepared the Luteinising hormone, (LH). FSH has also been called "Prolan A" and LH "Prolan B".

FSH stimulating the granulosa and ova and the male germinal cells. LH acts on the theca and interstitial cells of the ovary and the interstitial cells of the testis.

The Leuteotrophic hormone (LTH) described by Gruter and Stricker (1929), induces lactation only if the mammary glands have been brought to full development and must not be confused with development of the mammary glands which is due to ovarian secretions. Riddle et al (1933) have worked at length on this hormone which they term "Prolactin".

It seems clear that the gonadotrophic hormones have a definite effect on the growth, by inhibiting the growth hormone acting on the gonadal hormones at the attainment of puberty. The period of active growth is thus ended and epiphyseal closure, ensues. The tallness of the eunuch is the result of the absence of the growth inhibiting effect of the gonadal hormones and the persistence of active growth through the failure of epiphyseal closure, Schour and Massler (1943).

#### The Posterior Lobe and its Hormones.

The Posterior Lobe is of nervous structure and probably functions together with the hypothalamus, with which it is connected. It contains basophil cells which provide its active principle called "pituitrin" or "hypophysin". According to Ham (1953) this contains:

- 1) antidiuretic hormone, failure of which causes polyurea and diabetes insipidus,
- 2) Oxytocin (Pitocin), which induces swift labour at the end of pregnancy by increasing smooth muscle tone especially in the uterus.
- 3) Pitressin, which has a hypertensive effect on the smooth muscle of vessels, causing vasoconstriction.

## HYPERPITUITARISM.

Preadolescent hyperpituitarism results in either normal pituitary gigantism which is characterised by generalised proportional enlargement of the body due to increase in both growth and sex hormones, or eunuchoid gigantism where disproportionate growth occurs due to relative deficiency of sex hormone secretion before epiphseal closure. Postadolscent hyperpituitarism is acromegaly, characterised by enlargement of the extremities. All are to be distinguished from hereditary, familial and racial gigantism. Thoma and Goldman (1960), Lisser and Escamilla (1962).

### NORMAL PITUITARY GIGANTISM.

Is due to early hyperplasia or adenoma of anterior pituitary resulting in greater secretion of both growth and gonadotropic hormones

### Clinical Features.

There is a proportionate excessive growth of the tissues beginning in childhood or early teens, and also there is usually an excessive sexual activity at first which diminishes later. This "burned out" later phase is seen in diminishing strength, mentality and alertness resulting in death usually between 20 and 30 years.

Lisser and Escamilla (1962) state from their record of thirty cases that height of these giants vary from six foot eight inches to nine feet, but usually are between seven to eight feet, and their weight is usually over 300 lb. During the "burned out" phase these figures are usually reduced. Headaches and impaired vision are common symptoms.

### Cranio-facial and dental development.

Thoma and Goldman (1960) point out that head and neck development is proportionate to the rest of the skeleton, Large teeth, with long roots, and which are yellow with hard enamel and dentine, and tending to be well spaced is usual. Hutton (1936) recalls a case of a female giant 20 years old, whose teeth were nearly all broken off at the gingival margin, and that in his experience generally the teeth of giants are poor in quality. This may be due however to a condition of oral neglect associated with the diminished mentality often found in giants.

With the onset of symptoms rarely before the age of six years in pituitary gigantism, the crowns of the teeth of the permanent dentition are not affected as to variation in size, although the rates of eruption and exfoliation appear to be increased, Resch (1958)

Thoma and Robinson (1955) remark that the jaws may be large, but since morphodifferentiation of teeth takes place early, the teeth usually are normal in coronal size, with spacing and enlarged roots. Hypercementosis may occur producing enlargement in the roots.

## EUNUCHOID GIGANTISM.

This condition is due to pituitary adenoma causing excessive growth hormone secretion but diminished gonadotrophic hormone secretion. Probably due to the basophil cells being suppressed by the enlarged acidophil component, Thoma and Goldman (1960).

### Clinical Features.

The eunuchoid giant is of disproportionate dimensions, the lower measurements exceeding the upper. Continued growth of the long bones, because of the existant hypogonadism preventing closure of the epiphyses coupled with growth hormone oversecretion, results in very long arms and legs.

Englebach (1932) stated that maximum growth occurs before the early adolescent years and the abnormal growth of the long bones occurs many years after adulthood. Hypogonadism is secondary, the pituitary gland disorder being the prime factor. Absence of obesity, underdevelopment of musculature, with external genital hypoplasia in male and absence or diminution of menstruation in female are the usual features of the condition.

### Cranio-facial and dental development.

Englebach (1932) states that the upper first incisors are enlarged and the second incisors are either rudimentary or absent. Lissner and Escamilla (1962) also report a case of missing lateral incisors. (See Eunuchoidism, under Hypogonadism for further details).

**Fig. 1**

Normal pituitary gigantism. Age 43, Verified height 7'6½"; Weight 359 lb. The doctor beside patient is 5' 9½". The patient died of uraemia at age 44 yrs. In contrast to most giants, was healthy and energetic businessman.

Lisser and Escamilla (1962).



**Fig. 2**

Eunuchoid Gigantism. Age 18 years; Weight 216 lb.; Height 7' 1½"; span 6'11". Bone age of 14 years.

Thoma and Goldman (1960).





Fig. 2.

Acromegaly of 25 years duration. Photographs taken at the ages of 16, 20, 29, 33, 39, 45 at autopsy. Shows unimpeded progression of facial changes.

Lisser and Escamilla (1962).

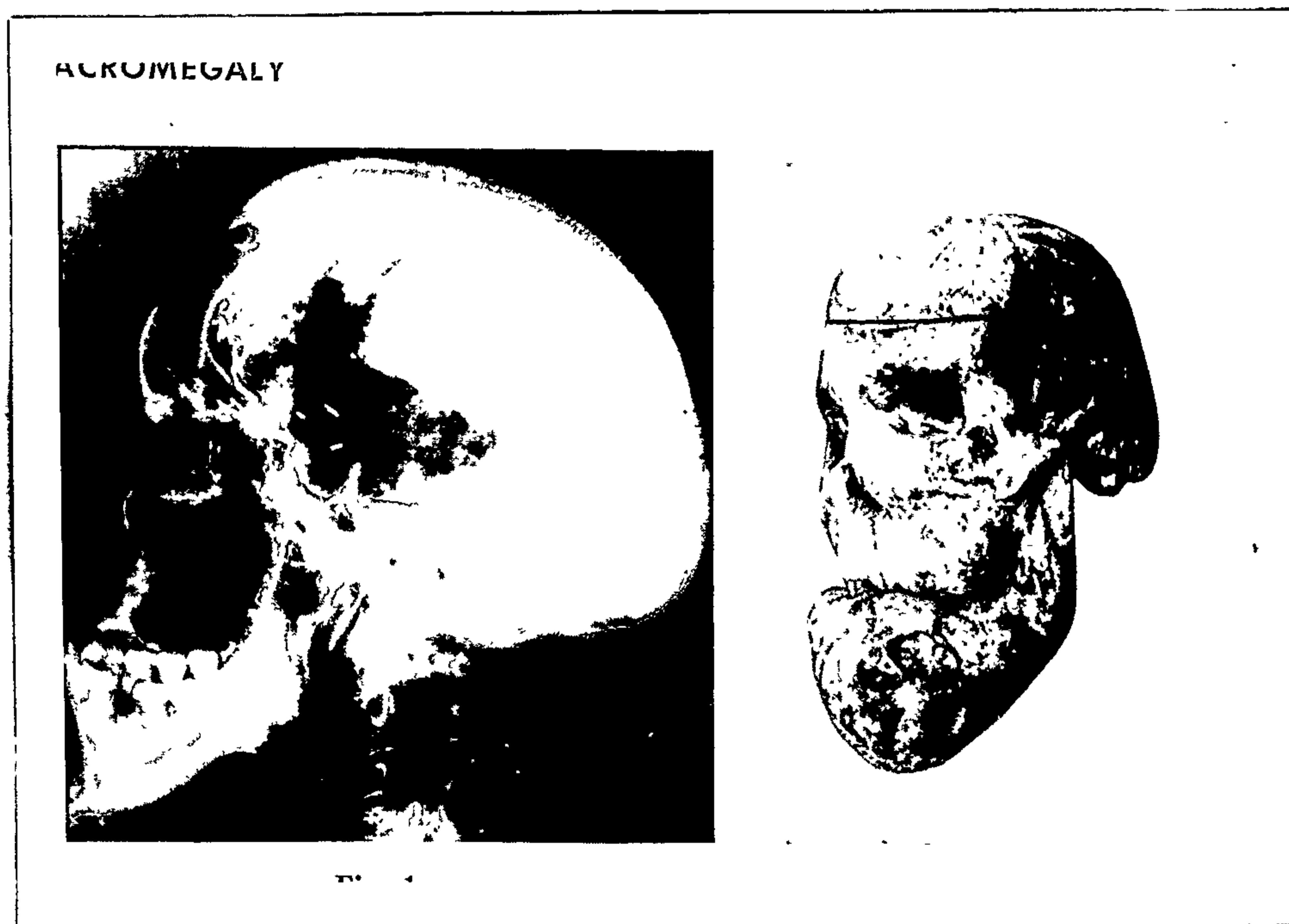


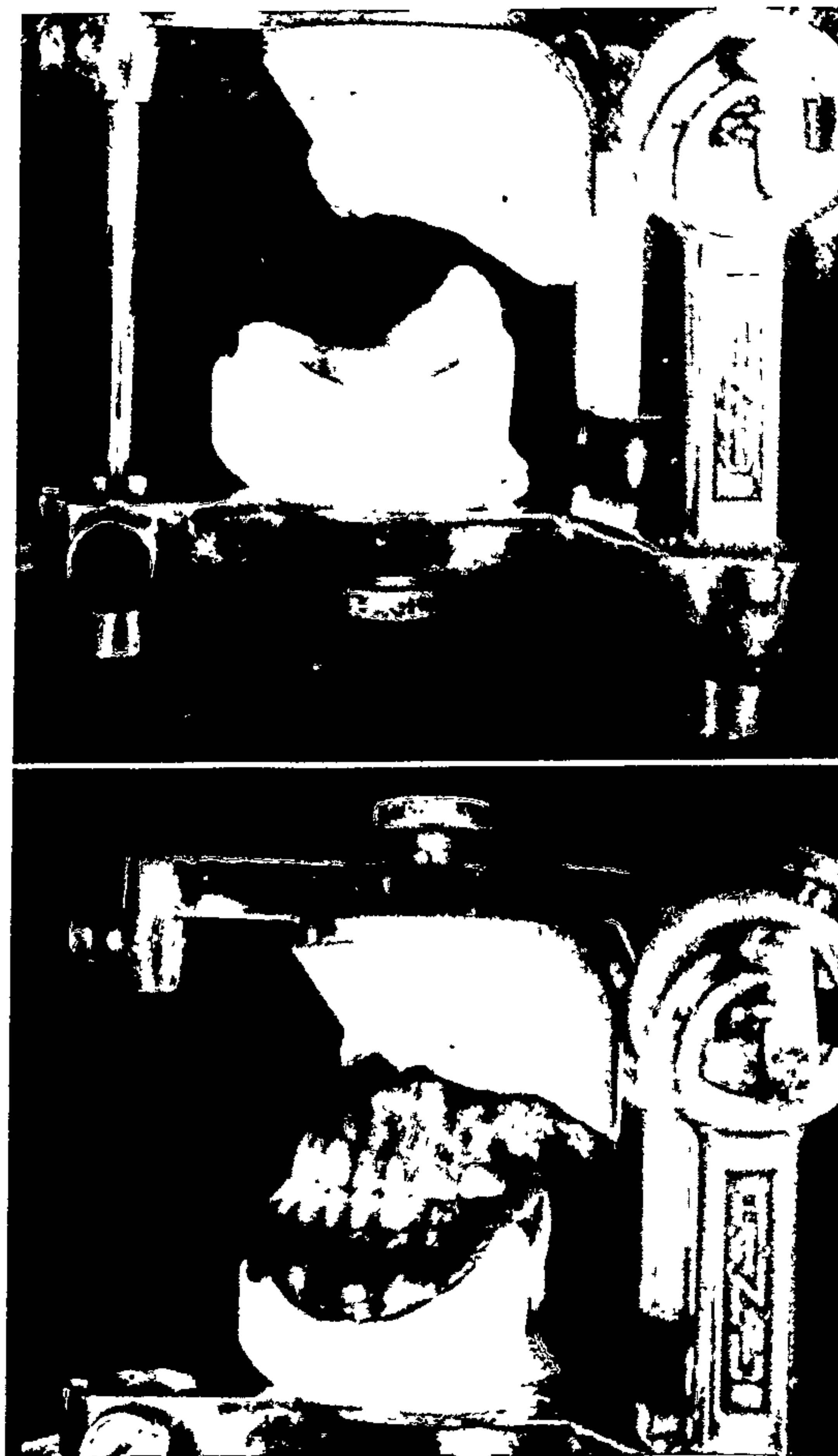
Fig. 3.

Acromegaly. Radiograph shows much enlarges sella turcica, huge sinuses, marked prognathism, enlarged mandible etc. Skull of acromegaloid giant, showing marked prognathism, enlargement of mandible, hyperostoses.

Lisser and Escamilla (1962).

**Fig. 5**  
**Acromegaly. Enlargement of the mandible and spacing**  
**of the teeth. Colby, Kerr and Robinson (1961).**

**Fig. 6.**  
**Acromegaly. Set-up of teeth**  
**on the articulator in a case**  
**of full denture prosthesis.**  
**Note prognathism and the bite**  
**Sackerman (1955).**



ACROMEGALY.

Acromegaly was first discovered by Marie (1886), and was called "Marie's Disease".

The disease is simply postadolescent hyperpituitarism, and is a rare condition generated by the same pathologic changes that cause normal gigantism, only the onset is later occurring between the ages of 20 and forty years. Lisser and Escamilla (1962), state that it occurs in 40% of cases of gigantism, as superimposed, due to failure of the adenoma to cease causing excessive secretion, after adulthood is arrived at. However, the classical case occurs after epiphyseal closure, therefore the long bones are not affected. Extensive experiments on animals have proved the above remarks and will be considered later.

Clinical Features.

Acromegaly means "large extremity" which is seen in overgrowth of the short flat bones, such as forehead, chin, superciliary ridges, cranial vault, terminal phalanges of hands and feet. There is also consequent enlargement of the face, lips, tongue, nose, ears and skin and hair becomes coarse. The head takes a hexagonal shape, and there is marked prognathism. Increased perspiration and night sweats, and warning of sexual activity preceded by earlier increase, of it, are common and important symptoms. Bitemporal headaches and photophobia are other features usually present. Diabetes Insipidus and Diabetes Mellitus are complications that sometimes occur. Following the period of rapid growth, is a "burned out" phase of the disease associated with hypopituitarism. Lisser and Escamilla (1962).

Davis (1940) found that the Thyroid gland frequently is enlarged, elevating the metabolic rate in a study of 166 cases. Resection of the thyroid led to reduction in the metabolic rate. Three cases of acromegaly associated with amyotrophic lateral sclerosis were reported by McCullagh and Hewlett (1947).

Histological Examination.

Stones (1954) states that the essential change in the affected bones is an increased thickness due to subperiosteal deposition.

There is also an increased osteoblastic activity in the spongiosa leading to thickening of the trabeculae. The result of all this is increased density. Thoma and Goldman (1960) indicates that the hormone causes an activation of periosteal osteogenesis, occurring especially at muscle attachments such as with the ascending ramus, which often shows up radiographically as denser bone than usual. Histologic investigation shows a hyperplasia of gingival epithelium as well as a hyperplasia of the collagenous connective tissue. The glands, especially the sebaceous glands, may become enlarged, Thoma and Robinson (1955), Thoma and Goldman (1960).

#### Radiographic Examination.

The appearance of the sella turcica is of diagnostic importance, enlargement or destruction of which, indicating a pituitary tumour. Another feature is the very much enlarged sinuses and the changes in the mandible mentioned above. All affected bones are inclined to show greater radiopacity.

#### Cranio-facial and dental development.

Hutton (1936) comments that acromegaly may be suspected by the dentist before anyone else sees the patient. One of the first conditions that bothers the acromegalic as an increasingly troublesome malocclusion. The dentist who recognises this will render the patient a great service by recommending early treatment.

The nose becomes enlarged, the lips become thick and coarse and of Negroid character, especially the lower lip, the condition of which is worsened by the progressive protrusion of the mandible. The skin becomes thickened, the pores are large and hyperhidrosis and seborrhoea are commonly seen and the hair becomes coarse. Simpson (1936) made investigations of the tongue in Acromegaly, and indicated that the enlargement of the tongue contributes to the flaring out of the teeth, spacing and the subsequent malocclusion.

In the later stages of the condition neuralgia of the fifth cranial nerve with associated headaches, and dull pain of the jaws often occurs Nachlas (1951).

Prognathism with associated malocclusion due to accelerated condylar growth (the hormone affecting site of endochondral rather

than membranous bone formation) and the mandibular angle taking on a more obtuse form may be quite extreme, Thoma and Goldman (1960), and Lissner and Escamilla (1962). Reade and Brown (1963) comments that in acromegaly a classical clinical picture is seen in which mandibular prognathism is an important part, and although the condyle is enlarged temporomandibular joint disturbances have not been reported. The prognathism and enlargement of the arches causes bad malocclusion causing difficulty in mastication and if patient wears dentures, labio-buccoconversion. This was first believed to be due to interstitial growth of the jaw but is more likely a result of pressure exerted by the enlarging tongue, Simpson (1936), Thoma and Goldman (1960). In association with the prognathism the angle of the mandible usually becomes very obtuse, and may be up to  $130^{\circ}$ , Stones (1954).

Howard (1937) in an interesting survey, described an acromegaloid type of child with advanced skeletal growth due to hypersecretion of the growth hormone, not of congenital origin as in normal gigantism but caused by a postnatal influence, causing the production of qualitative, or quantitative abnormality of the growth hormone. Such patients show acromegaloid abnormalities of the face, especially overgrowth of the mandible, causing Class III malocclusion with spacing of the teeth. The characteristic skeletal abnormalities of acromegaly are lacking in degree or occur later if the disease continues after the age of maturity. Fifty-nine patients with hyperpituitarism, ranging between the ages of five and 20 years, (most patients being between 10 and 17 years of age), were examined by Howard with the following result:

Number with acromegaloid growth (Class III).....	13
Number with advanced acromegaly (Class III).....	1
Number with excess arch width, otherwise normal.....	6
Number with normal arch and jaw development.....	36
Number with slight deficiency in arch width.....	1
Number with retarded growth of mandible (Class 2, Div 1).....	1
Number with normal arch and jaw growth (Class 2, Div, 2).....	1

Mandibular prognathism is not always found in acromegaly. Korkhaus (1933), pointed this out citing four cases of acromegaly to show that while in advanced cases the dental arches, especially in the mandible show pronounced enlargement, mandibular protrusion of the teeth does not always result. He also said that the forward tilting of the lower teeth was probably due to the enlarging tongue. Korkhaus (1955)

reported findings on 13 other patients, four of which had normal overbite in spite of greatly enlarged cranial dimensions; four had edge-to-edge bite; and five had the typical prognathism. In all patients he found an overdevelopment of the condyle and ramus, besides tilting and spacing of the teeth, and marked hypercementosis.

Becks et al (1944, 1946, 1948) in a series of excellent experiments on hypophysectomised rats, found that growth processes in these animals senescent mandibular joints, could be restored to juvenile vigour by pituitary growth hormone administration, because some uncalcified cartilage remained in the condyle for long periods in both the hypophysectomised and normal rat, and thus conferred upon the joint the capacity for growth and remodeling.

There is no connection between ordinary prognathism, which is mostly due to hereditary factors, and the acromegaloid type. The acromegalic type is distinguished by the other general acromegalic symptoms, and disturbance in the endocrine balance, and an enlarged sella turcica. Conversely it is pointless to attempt to treat cases of retruded mandible by endocrine therapy because of the fact that anterior lobe hormone is selective in its action and when given may cause serious somatic disturbances.

Keith (1911), made the interesting comment that, in a sense, acromegaly is an accentuation of the normal growth pattern, prolonged in time. Theoretically one living to an age of 200 years would attain the acromegaloid features of the face. Keith (1911) examined all the acromegaloid skeletons in London and concluded; the width of the last molars is increased in the mean by nearly 100mm, so that the right and left lower molars being nearer together than the upper molars, are wide apart and project beyond the dental arcade. The canines are advanced so as to come more nearly into a transverse line with the incisors.

#### Treatment.

In hyperpituitarism, deep X-ray therapy of the pituitary is the preferred line of treatment and is detailed by Lisser and Escamilla (1962). They also allude to partial hypophysectomy if vision is treated or other serious "neighbourhood signs" develop, and also hormone therapy employing the androgens in males and estrogens in females. Kerr (1948) gives the results of irradiation of pituitary tumours in 50 patients, Sheline (1961) makes similar investigations of

irradiation therapy in the treatment of acromegaly.

Prognosis is good, if the disease is treated early.

#### Dental Treatment in Acromegaly.

In view of the discomfort usually associated with this condition, an attempt to alleviate some of the oral manifestations can be gratifying to both the patient and the dentist. Very little has appeared in the literature as to this, but the article of Sackerman (1955) is of special interest. One of the greatest problems confronting acromegalics is ill-fitting dentures, due to the increasingly enlarged mandible. Sackerman (1955), considers this question of complete denture prosthesis for acromegalics very well. Other factors which have to be considered in the matter are subnormal muscle tone, thickened lips and an enlarged tongue. The pronounced mandibular prognathism necessitated eight lower incisor inclined posteriorly to give an edge-to-edge bite, and a bilateral cross-bite. Sackerman (1955), concluded with the following remarks;

1. Full denture prosthesis for the acromegalics is a field deserving attention.
2. The disability and complex ramifications of the disease makes necessary an efficient masticatory apparatus.
3. Although clinically, the unfavourable, outnumber the favourable conditions, dentures can be made for an acromegalic.
4. The prosthetic procedure differs from the average case, mainly in the setting of the teeth and the plumping of the dentures.
5. An acromegalic can derive the benefits of both aesthetics, and function from full-denture prosthesis.
6. A six-month recall system would detect an exacerbation of the conditions and determine the need for readjustment or reconstruction of the dentures.

## EXPERIMENTAL HYPERPITUITARISM.

Daily intraperitoneal injections of an aqueous solution of anterior pituitary lobe extract into immature rats, have produced gigantism. The changes become very noticeable during the postpubertal period. A weight about double the normal of 700 grams for females and 900 grams for males was achieved, Evans and Long (1921). Injections into 21 day old mice have also promoted a general increase in growth and the size of jaws and teeth, incisor teeth being markedly larger. The rate of growth of the incisors is also accelerated from the normal rate of 1mm per week in the controls to 1.3 mms in those receiving diurnal injections. Histological examination of the incisors, molars and jaw bones shows no abnormality in structure, Downs (1930).

Becks, Collins, Asling, Simpson and Evans (1947) found that an acromegaloid type of gigantism was induced in 8 normal female rats by daily injection of growth hormone for 437 days after their growth curves had plateaued. Their skeletons and teeth were compared with five controls. Radiographic examination showed that the skull and dentition were decidedly larger, bone structure was denser and sinuses were enlarged. The mandible showed continued osteogenesis with hyperossification, exostosis and distortions in form of the neck and head of the condyle. The teeth were not only larger, but also the incisors showed interglobular dentine in numerous areas, whilst the molars showed larger and longer roots and an unusual degree of hypercementosis.

With 4 weeks old bulldogs the experiment produces an acromegalic gigantism with larger jaws than the controls. Putnam et al (1929) and (1930) discovered this in a very interesting piece of work. The bulldog was given daily intraperitoneal injections of sterile anterior lobe extract, 10mls. After three weeks, it became apparent that the dog was growing more rapidly than the control from the same litter. The daily injections was increased to 20mls then to 30ml., then 40ml on the 50th week, and soon after to 50ml. About the 60th day soon after the dose was increased to 75ml the dog died and the control was sacrificed. The experimental animal weighed 44kg, and the 23. 3kg. Other changes in the injected animal were, enlarged skull, walls of frontal sinuses thicker but sinus cavities no larger, the lower jaw was greatly increased in size especially in length, the teeth were longer and the interdental spaces were larger and longer and the tongue was

much enlarged.

Downs (1930) using fox-terriers, 8-10 weeks old, compared the results of three groups; hypophysectomised animals, animals having anterior lobe injections, and controls. The last group developed an acromegalic gigantism but with normal structure and size of the teeth. He considered that in animals having diphyodont dentitions, their size and form seem to be laid down in accordance with genetic principles entirely and are consequently little if at all influenced experimentally.

Growth of the oral tissues has been stimulated by the administration of stomatotrophic hormone (STH), by Becks et al (1946), (see Experimental Hypopituitarism) Baume, Becks and Evans (1954), McKenzie and Avery (1958), Stahl, Gerstner, and Joly (1958), and Stahl and Joly (1958), and again Stahl, Gerstner and Joly (1959). In this last mentioned study, Stahl et al (1959) report the results of their findings as follows;

- 1) The oral epithelium at the site of injection showed an acanthosis and an increase in binucleated cells in the prickle cell layer.
- 2) STH administration inhibited the osteoporotic changes in both the alveolar bone and the femur observed in the control groups fed a protein-free diet. The periodontal membrane of the STH treated group showed greater cellularity than was observed in the periodontal membrane of the animals fed a protein-free diet, alone. This was a similar result to that of earlier experiments, (on rats fed a normal diet) .

These results were in agreement to those of Bavetta, Bernick, and Ershoff (1956) who demonstrated similar maintenance of osteogenesis and chondrogenesis in tryptophan-deficient rats receiving STH.

Becks and Riebe (1961) studied the effects of ACTH on the osseous system of rats, particularly on the tibia, and the healing of post-extraction sockets. The female rats injected with ACTH showed marked loss of weight and retardation of growth. The rats injected for long periods showed a progressive, orderly reduced density of the bone. The absence of osteoblasts and osteoclasts on the trabecular, endosteal, and periosteal surfaces suggest a reduction in osteogenic processes.

It is well known that hypercortisonism causes an osteoporosis, and the above results may indicate that it is due to an increase in ACTH production in certain cases. (See "Bone changes in oral region" in the section on Cushing's Syndrome.)

Washburn (1956) questions whether the rat is the best animal for experimentation with the Growth hormone, as its growth pattern is different to that of man. He also states that the rat's jaw is a very difficult one to use if we want to transfer the results to man. He suggests that the tree shrew is a more suitable animal, which simulates man's growth pattern much more closely.

**HYPOPHYSEAL INFANTILISM.**

Hypopituitarism in infancy causes Hypophyseal infantilism, (or Pituitary dwarfism, or Levi-Lorain infantilism), and in adults causes Simmond's Disease )or Extreme insufficiency of the adenohypophysis, or Sheehan's syndrome).

**HYPOPHYSEAL INFANTILISM (Pituitary Dwarfism, Levi-Lorain Infantilism)**

This is not the only type of Dwarfism, as indicated by Lisser and Escamilla (1962), who gives a differential diagnosis chart of ovarian agenesis, with sexual precocity, Achondroplastic, and Primordial types. Thoma and Goldman (1960) state that also hypopituitarism does not necessarily produce dwarfism, not even if the deficiency occurs at an early age. They state that Pituitary dwarfism is produced only in the case of deficiency of the secretion of the acidophil cells of the anterior lobe, which produces the growth hormone, and then only if it occurs before full stature is attained. The most marked cases are those with their inception before adolescence. Lisser and Escamilla (1962) remark that the condition is due to a moderately diminished function of the anterior pituitary glands, and that it is not rare especially in its milder form. They state that the pathologic lesion may be either idiopathic hypoplasia of the pituitary, or pressure on the anterior lobe by a tumour (such as Rathke's pouch cyst or very rarely a chromophobe adenoma). The hypofunction of the pituitary is congenital, and the growth and gonadotrophic hormones are both affected. Muir (1951) remarks that in many cases of pituitary dwarfism no evidence of a tumour has been found on X-ray examination.

**Clinical Features.**

According to Lisser and Escamilla (1962) the important physical signs are; shortness of stature; primary sex characteristics retarded or infantile; greatly delayed appearance, absence or underdeveloped secondary sexual characteristics at ages when these should be manifest, youthful childish features; look many years younger than normal children of same age, but occasionally the face may

look somewhat older than rest of body due to fine wrinkling. They also state that other signs are retarded dental development, with teeth likely to be small and crowded and that the palatal arch is high and narrow; retruded mandible, skin delicate and of fine texture and sometimes wrinkled; underweight rather than adipose features which is in contrast to Frolich's Syndrome).

Lurie (1938) states that the pituitary dwarf is mentally alert however, and tends to be forward and aggressive and to dominate his environment. Thoma and Goldman (1960) state that some are born small and some normal size. Usually there is not much change in the first five years, except a reduction in height. Higgins (1936) reported a case of pituitary dwarfism in a male child who weighed 3lb 7oz at birth, at the age of 1½ years he was 26" tall instead of the normal 31" and weighed 10lb instead of the usual 24½lbs, and his head measured 16¼" instead of 18¾". X-ray films of the long bones showed normal structure and epiphyseal development. His teeth were sound but small.

#### Cranio-facial development.

Schour and Massler (1943) remark that the effect of hypopituitarism on the cranio-facial skeleton is in harmony with the effect on the whole body skeleton. The cranium and face develop very slowly and resemble those of a child of a much younger age. The face is characteristically small especially when compared with the cranium. The paranasal sinuses, particularly the frontal are underdeveloped.

#### Growth of the jaws.

Cushing (1912) believed that deformation with forward displacement of the sphenoid bones slightly increases the prominence of the maxilla so that maxillary prognathism results. However, Schour and Massler (1943) state that this jaw relationship commonly seen in dwarfs is simply an accentuation of the normally retruded mandible of the infant and that it may be explained on the basis of the slowing down of the growth of the condyle, which is normally the site of the most rapid growth after the body of the mandible is formed. Lisser and Escamilla (1962) remark that the clinical picture is the opposite to that of acromegalic prognathism, and that there is retarded dental development and a high narrow palatal arch.

Kingsley (1891 and 1879) gave details in a very interesting article of the well known dwarf, Charles S. Stratton, known as General Tom Thumb, who was born in (1832) and died in (1883). He was 9lb at birth, at 5 months he was 25" tall and he weighed 15lb. In the following 13 years, he gained only 2oz and never grew any taller. He had a childish feeble voice, vivacity of expression, and was generally cheerful. Tom Thumb had very undersized jaws in harmony with the rest of his osseous system, but he had teeth the size of a normal man, resulting in gross malpositioning, so much so that he was said to have "a double row of teeth all round".

Marinus (1934) and Hutton (1936) both state that pituitary deficiency in childhood plays no part in any orthodontic problem. As the child approaches puberty, there may be some increase in growth, which does not affect the body equally in all its parts, with the result that the mandible may develop little or not at all, while the maxilla may develop normally. They also state that under pituitary medications there is definite stimulation of growth with widening of the arch, such as ordinarily occurs with orthodontic appliances.

Stones (1954) states that the jaws are very small both in vertical dimension and arch length.

Crigley et al (1962) studied dento-facial growth retardation in hypopituitarism by the cephalometric tracing.

#### Development and eruption of the teeth.

In addition to the investigations of Kingsley (1897, 1891) as to "Tom Thumb above mentioned, there is a report of another historical case of infantilism, Caroline Crachami, whose skeleton is in the Royal College of Surgeons Museum, and who at the age of 9 years was the size of a child less than 15 months, by Brash (1929). He stated that the patient had an irregular dentition comparable to that of a child of 2 years. Englebach (1932) however remarked that in anterior lobe deficiency, the teeth are usually miniture, comparable to the diminution of the body as a whole. Schour and Massler (1943) wrote that the dentition is in keeping with the skeleton age, and as judged by the eruption is retarded and shedding is delayed in harmony with the retardation of the growth of the body in general. They mention that a hypopituitary patient of eighteen chronologic years of age, and

skeleton age of eight would show a dentition age of typical eight to ten years old child. They do not agree with those who say that the teeth themselves are smaller, their theory which seems to be right, being that the clinical crowns of the teeth alone are smaller, the smaller arches causing this, whilst the anatomical crowns remain normal size.

Thoma and Robinson (1955) state that the teeth of pituitary dwarfs differentiating early than the initiation of the pituitary insufficiency, are usually of normal size crowding small jaws.

Resch (1958) remarks that the retarded eruption and shedding is probably due to the secondary hypothyroidism, which is often present.

The roots are usually seen as incomplete, with wide apical foramina (Schour and Massler (1943)).

Marcus et al (1942) studied facial development in pituitary dwarfism in a group of 8 patients by means of Hellman's linear facial standards, Salzmann (1950), and found no retardation of eruption in their study. However they did not ascertain how much and how long endocrine therapy was given these patients. Although malocclusion was found in all cases no classification was found to be pathognomonic. Root formation and closure of the apices were found to be delayed and the pulp chambers were characteristically wide. Gordon and Kuskin (1935) stated that delayed onset of teething in the absence of signs pathognomonic of other diseases in children indicates endocrine disturbance. Salzmann and Wein (1952) remark that while it does not seem likely that endocrine disturbances in children can produce dental disturbances without showing evidence in other parts of the body, transitory and subclinical endocrine disturbances may possibly influence the dentition without showing marked general development disturbances. Although the formation, development and eruption of the teeth can be influenced by endocrine dysfunction, the dentition is not to be accepted as a sole pathognomonic sign. Additional diagnostic aids must be relied upon in establishing a diagnosis of endocrine dysfunction. Howard (1937) made similar comments as to this.

Over calcification of the cranial bones and the dentine in pituitary dwarfism has been reported by Schour, Brodie and King (1934), Mortimer (1937) and Goldziezer (1934, 1940). Cohen and Wagner (1948) in studies on two individuals with pituitary dwarfism over a

long period of time reported that their teeth calcified normally, whilst there was a bone growth delay, and retarded eruption.

#### Treatment.

Salzmann and Wein (1952), reported a case of pituitary dwarfism where thyroid therapy was given for four years without much success, but when methyltestosterone was administered the patient's height and bone age showed an appreciable rise. Lisser and Escamilla (1962), remark that anterior pituitary growth hormone (purified from beef or pork) so far has been ineffective in humans, evidently because of species antagonism. However human growth hormone is now available and seems effective, but supplies are limited. Raben (1958), Hutchings et al (1959), Escamilla et al (1961). Potent sex hormones such as testosterone are the most effective means of treatment, and are advisable because they do not cause premature bone maturity in the recommended doses. Oestrogen therapy is given to assist sex maturity in girls.

Green (1951), gives a report of treatment of ten cases.

Prognosis. of dwarfism is good, usually unless complicated by pituitary tumour.

SIMMOND'S DISEASE. (Extreme insufficiency of the adenohypophysis, hypophyseal cachexia, Sheehan's syndrome.)

Simmonds described the disease in (1914, 1916, 1919), and reported 21 cases.

Muir (1951) remarks that this is the commonest and most important example of anterior lobe hypofunction. It develops as the result of a destructive lesion of the pituitary gland, and occurs far more frequently in women than in men, and often follows pregnancy or abortion, particularly when associated with post-partum haemorrhage, Conybeare and Mann (1952).

A benign tumour (chromophobe adenoma or craniopharyngioma) or malignant tumours (metastases from carcinoma of thyroid or breast), trauma due to skull injury or infection (abscess, syphilis, tuberculosis), diabetes are all causes of the condition, in addition to those following post-partum haemorrhage with consequent shock, causing infarction and necrosis and more or less severe hypopituitarism. Lisser and Escamilla (1962) however indicate that this has not fully been demonstrated, and the clinical picture has become known as Sheehan's Syndrome, Sheehan et al (1938, 1949, 1951).

Clinical Features.

Both Conybeare and Mann (1952) indicate that when present extreme general emaciation (pituitary cachexia) is the most striking symptom but is not always present, and the most consistent and conspicuous symptom is the total loss of pubic and axillary hair, and gonadal atrophy, which is due to early sex failure in the disease.

Lisser and Escamilla (1962) state that the important symptoms and signs are:

1. Loss of sexual function and atrophic changes in genitalia,
2. change in weight,
3. asthenia and weakness,
4. loss or thinning of sexual hair,
5. failure to lactate after a complicated parturition may be the first sign of impending Sheehan's syndrome, and is probably due to lack of prolactin,
6. dryness of skin,
7. dental caries and loss of teeth.

## 8. hypotension.

Cranio-facial and dental development.

Lisser and Escamilla (1962) state that dental caries and loss of the teeth is a feature of the disease.

Silver (1933) also states that Simmond's disease is sometimes associated with caries, and even teeth loss without caries.

Thoma and Goldman (1960) add that there are facial changes seen in thin eyebrows, loss of eyelashes, sharp features, thin lips, wrinkles and an immobile expression, and that death occurs from premature senility,

Differential diagnosis; from Addison's Disease, with which it is often confused is important. There is striking pigmentation and gastrointestinal distress associated with Addison's Disease rather than in Simmond's Disease, and the early loss of sexual function is more suggestive of Simmonds Disease, Lisser and Escamilla (1962).

Treatment.

In Simmonds Disease endocrine therapy lengthens life, such as androgens, oestrogens, cortisone, ACTH, Thyroid if myxedema is present, is advised. Prognosis is that the disease is usually fatal though course may be extended over many years, in a chronic form. Lisser and Escamilla (1962).

PITUITARY MYXEDEMA.

This condition has been described by Lisser and Escamilla(1962) Means et al (1940), Escamilla (1955) and De Candia (1958).

According to Lisser and Escamilla(1962) it is due to extreme insufficiency of the anterior lobe of pituitary, differing in that the patient looks decidedly myxedematous and either loses little weight or actually gains. Many patients with Sheehan's Syndrome (post-partum necrosis of the anterior pituitary) develop this appearance. Differentiation from true myxedema is important, as the reaction to thyroid substance may be quite different; also prognosis of this condition is likely to be poor. The condition is actually a sub-type of Simmonds Disease, and manifests many of the same characteristics.

Early loss of sex function as in Simmonds disease and failure of lactation are important symptoms.

Puffy bloated myxedematous appearance of face, dryness, of skin, and thinning or absence of sexual hair and eyebrows are other signs.  
Cranio-facial and dental development.

In addition to the myxedematous appearance of the face, Lisser and Escamilla (1962) also include dental caries and sometimes loss of teeth are signs of the disease.

Treatment.

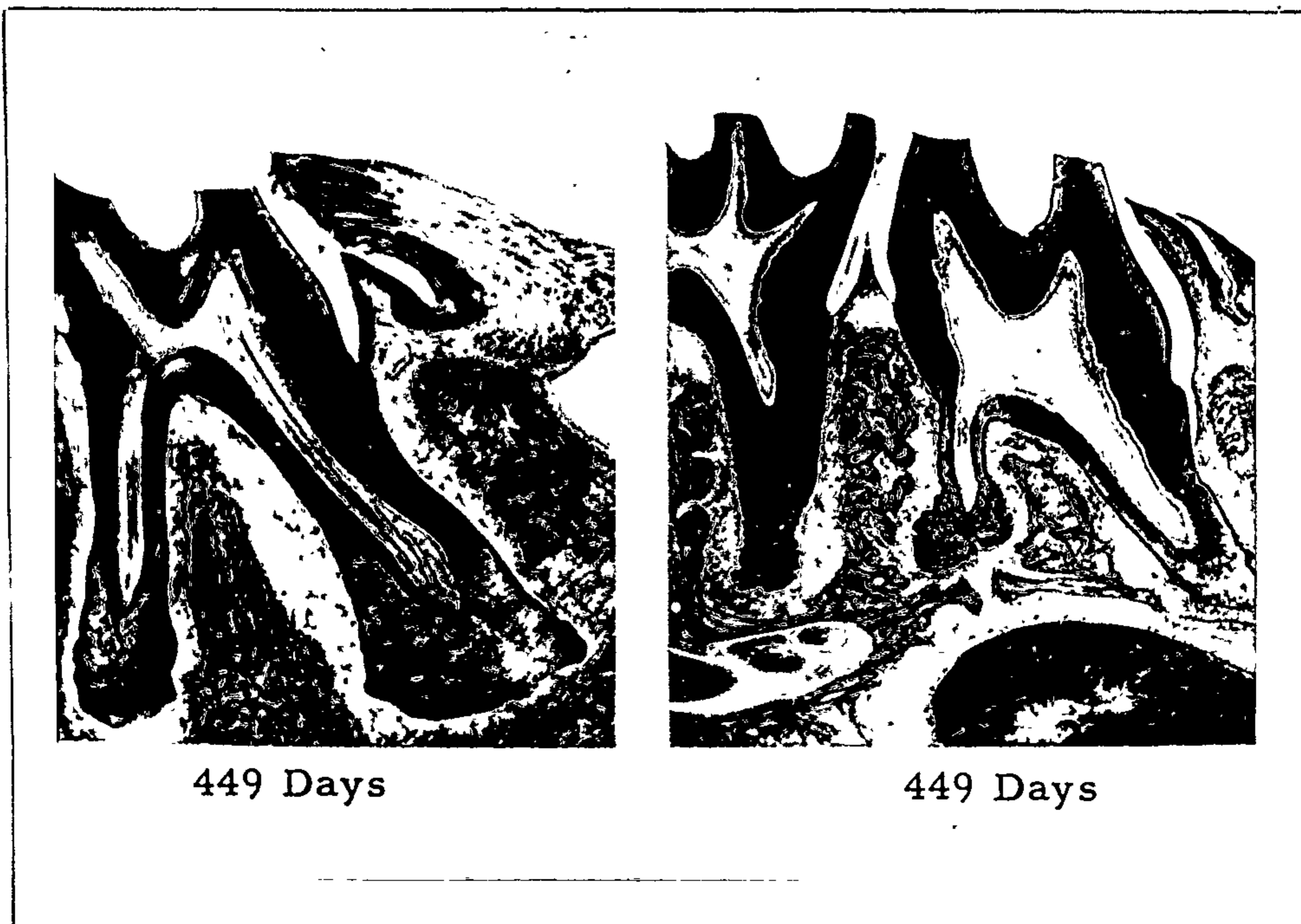
Similar to Simmonds Disease. Thyroid should be used cautiously for the reasons indicated, but is occasionally helped when used in conjunction with methyltestosterone or adrenal cortical steroids.

The condition is usually fatal but may become extended over many years. In rare instances a subsequent uncomplicated pregnancy has revitalised the pituitary resulting in cure or amelioration of the previous hypophyseal failure, Lisser and Escamilla (1962).



Fig. 7.

Normal and hypophysectomized rat (Long-Evans strain) at the age of three months. Becks and Evans (1953).



449 Days

449 Days

Fig. 8.

Normal and hypophysectomized rat, lower third molar at age 449 days after hypophysectomy. Becks and Evans.



Fig. 9.

Normal rat upper incisor. Age three months.  
Becks and Evans(1953).

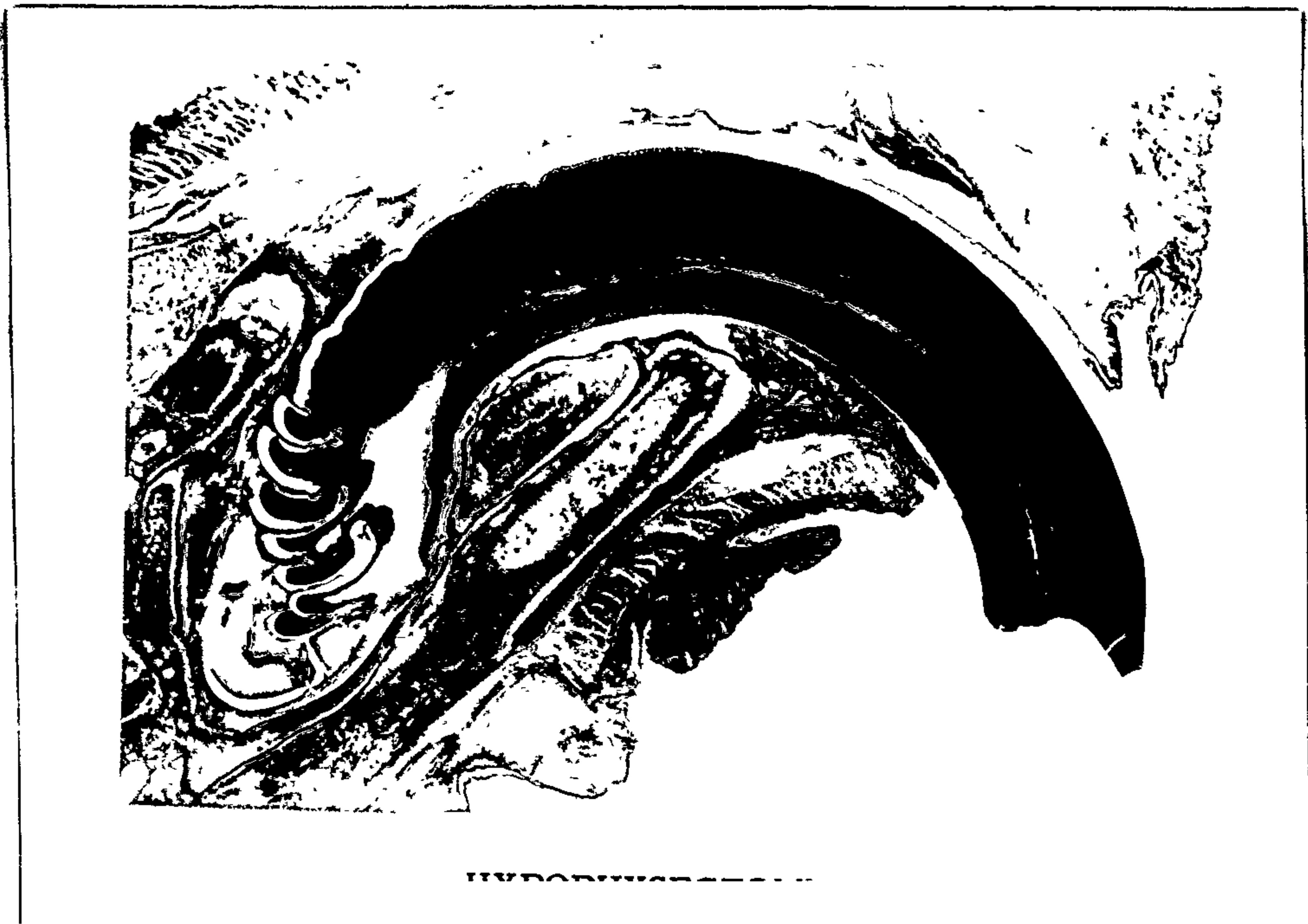


Fig. 10

Hypophysectomised rat upper incisor, 421 d,ys  
post-operatively. Note apical folding etc. See  
p.29.  
Becks and Evans (1953).

EXPERIMENTAL HYPOPITUITARISM. (Hypophysectomy).

The hazards of experimental hypophysectomy with early workers such as Paulesco (1891), Cushing and Morsley (1900-1911) were greatly reduced through the introduction of the parapharyngeal approach to the hypophysis by Aschner (1912) in dogs and Smith (1927) in rats. Since then, many successful experiments have been done in these animals and changes in the oral structures been observed.

Schour and Massler (1943) state that hypopituitarism in man is never so severe as complete hypophysectomy in animals. Hypophysectomised animals (rat, dog and monkey) show a marked deceleration in the growth of all tissues as seen in man. Smith (1927) showed that hypophysectomy in rats produces inhibition of growth and hypogonadism.

Effects of the growth and eruption of teeth: The effects of hypophysectomy on rat incisors were first assessed histologically and radiographically by Schour and Van Dyke (1932). They studied 23 rats which were hypophysectomised at between 34 and 64 days of age. In a postoperative interval of 63 to 459 days, progressive retardation of eruption was seen beginning from a week after the operation, arrested increase in the size (to about 2/3 normal size) and distortion of the form of the incisors constituted their general findings. Histologically the enamel epithelium was found to undergo regressive changes, ultimately leading to cessation of amelogenesis while dentinogenesis proceeded continuously obliterating the pupal cavity. Arrest of eruption and continuous dentine formation at the basal end, allegedly caused apical folding. The dentine showed many interglobular spaces and the cementum was thicker than normal. The pulp of the tooth was smaller with scanty blood supply, and the alveolar periostium was sprinkled with degenerated epithelial cells. Ten to fifteen months following the removal of the pituitary gland advanced changes occurred in that there was very little enamel, and that left was very poorly calcified, and multiple folding of the apex of the tooth at its basal end, and the dentine was not normal and contained many vascular inclusions. The periodontal membrane showed calcification of its fibres, and the dentine showed hypermineralisation, which is

characteristic of the over calcification associated with the experimental hypophysectomy. In the molar teeth changes were also observed, but in a different way to the incisors, Schour and Van Dyke (1934). The crowns of the molars were normal size since they were completed before the hypophysectomy, but juvenile characteristics persisted as evidenced by large pulps, incompletely developed roots, wide foramina and thin cementum.

Following these investigations it was inferred that hypophysectomy produces a cessation of the growth process from that of eruption, Schour and Massler (1943). Held (1944) in a study of early changes in hypophysectomy in rat incisors could not find alterations in dentine calcification but claimed decreased resistance to infection of the periodontal structures. Becks, Collins, Simpson and Evans (1946) in a study based on 143 hypophysectomised rats including post-operative intervals between six and 640 days concluded that a thickening of the dentinal walls at the expense of the pulp chamber was the only pathognomonic symptom of hypophysectomy. Distortion and folding of the apical tissues occurred inconsistently even among the animals which survived very long post-operative periods. This exhaustive investigation seems to clarify earlier conflicting reports.

Baume, Becks and Evans (1954) did some excellent research on thyroidectomised and hypophysectomised rats to ascertain the hormonal control of tooth eruption. They reported that the results of hypophysectomy demonstrated that amelogenesis and the activity of the odontogenic epithelium in particular depend directly on internal secretion, whereas dentinogenesis and cementogenesis are able to proceed at a depressed rate without the pituitary hormones. Working on 70 hypophysectomised and 70 control female rats of the Long-Evans strain they studied the growth and eruption of the upper incisors both metrically and histologically. The results of their survey were as follows;

- 1) In intact control rats a rapid increase in the radius of curvature was terminated at 120 days of age to be followed by a slow but steady gain until old age. The weekly eruption rate averaged 2.53m,m, and showed periodic variation and a decreasing gradient with increasing age.
- 2) Hypophysectomy affected an immediate drop of the eruption rate

to one half of the normal average; in ten weeks it was progressively reduced 76%. Stunting of the dental growth was noticed 2 weeks after operation so that the size of the incisor of 500 day old operated animals never exceeded that of 40-50 day old normal controls. Apical folding occurred in 60% of the operated animals 160 days after operation showing dysgenesis of inner enamel epithelium with enamel aplasia, disturbed calcification of mantle dentine and agenesis of odontoblasts. They suggested that the apical folding may be due to stresses of mastication acting on the little consolidated apical structures.

3) In the old operated rats the unfolded incisors were comparatively larger and maintained a minimal eruption rate in contrast to the folded ones which were smaller and had practically ceased erupting. This shows they state that eruption involves a basic process of growth

The generally more drastic effects of hypophysectomy in comparison to thyroidectomy, point to the action of a specific pituitary therapy. An interesting similarity of the folding of the apical third of the incisors of these hypophysectomised animals to the changes in the teeth of magnesium-deficient animals, was also demonstrated and they suggest the changes may be related to salt and mineral metabolism, thus implicating the adrenal glands and its mineralocorticoids. Muracciole (1957) found in his experiments on white rats, that the effect of hypophysectomy on the morphogenesis of dental structures, is moderate, and less than that of thyroidectomy. Irregular and insufficient calcification of the dentine was transient. Hypophysectomy and thyroidectomy greatly restrict the eruption and growth of erupting teeth. Eruption is completely arrested a few weeks after hypophysectomy. He concluded that growth and eruption of the teeth are controlled primarily by the hypophysis through the growth hormone, and secondarily by the thyroid through the action of the thyroid hormone.

Experiments have been done on other animals also, particularly Rhesus monkeys. Schour (1934), and Schour and Hoffmann (1935) published the results of their experiments on these and other animals. established the normal rate of dentine deposition at about 4 microns per day, and the calcification rhythm at about 16 microns per day. The technique for determining this was to inject peritoneally, 2%

alizeren red S at intervals. This dye was taken up by the blood stream and deposited on the newly formed dentine, which showed up in sections of the teeth as red lines.

Ziskin et al (1949) used this same technique with the injections being given before and after hypophysectomy on five monkeys. The above findings as to dentine and calcification measurements were confirmed and additional ones for hypophysectomised monkeys, following hypophysectomy the permanent teeth showed that dentine apposition in the occlusal region is retarded by an average of 49% and the cervical rate of 31%. The calcification rhythm and pattern of growth are also affected.

#### Replacement therapy on hypophysectomised animals.

Following Down's pioneering experiment (1930) Schour and Van Dyke (1932) found that replacement therapy if administered early was effective with a polyvalent hypophyseal extract in lessening retardation of eruption, and obtained a 0.4mm increased weekly eruption rate.

Collins, Becks, Asling, Simpson and Evans (1949) in some extensive work, showed that the chronic administration of pure growth hormone to hypophysectomised animals allowed the incisors to erupt but at only half the normal rate. The ameloblasts showed evidence of atrophy, but the dentine formed at a rate of 10 microns instead of the normal 16 microns per day. They were the first to use pure growth hormone.

Baume, Becks, and Evans (1954) further investigations on their hypophysectomised rats to identify with the help of replacement therapy, the specificity of the hormonal factors controlling tooth eruption, and assessed the response of the incisors of these animals to growth hormone and thyroxine and the combination of both. Their discoveries were;

- 1) Growth hormone resulting in an increase in size without hastening the eruption rate. Histologically there was a rejuvenation of connective tissues, without activation of amelogenesis. Growth hormone administered to normal animals had similar effects.
- 2) Thyroxin treatment increased the tooth dimensions and accelerated the eruption rate 36% in the young group and 46% in the older group of operated rats. Amelogenesis showed an improved pattern and the

vascularisation of the tissues was restored.

3) The combination of both hormones showed optimal effects in eruption rate and growth was characterised histologically by an amazing restoration of the completely atrophied enamel organ. These observations led to the conclusion that both growth and eruption is presided over by the synergism of two hormones; the pituitary growth hormone, which stimulates the basic process of growth, and the thyroid hormone which controls differentiation or maturation.

#### Effect on the Mandibular joint.

Collins, Beck, Simpson and Evans (1947) reported that the condyles in very young rats (5 days) are composed of hyaline cartilage. Under normal conditions this continues to grow but it becomes eroded by encroachment from the ossification centre, and in old animals it becomes mineralised except for a zone of embryonic cells. With hypophysectomy, 4 days after operation age changes are observed in the mandibular joint, 15 days after the ossification changes are comparable to a 106 day old normal control rat, and by 28 days, it is advanced as in a 258 day old normal control. Growth hormone given to rats which have been hypophysectomised for long periods at the rate of 200 mg daily for 30 days causes the senescent condyles to be restored to their youthful vigour.

#### Effects on the periodontium.

Eronke (1958) observed the effect of hypophysectomy on 120 female rats of different strains at Hamburg, on the periodontium of the rat molars. After the operation the animals were killed in groups of 20 from 1-180 days after the operation. Whilst dentine and enamel changes occurred after a few days, histological observable changes in the periodontial margin occurred three to four weeks after the operation. The clinical findings were as follows: retarded eruption, decrease in the length of roots, increased dimensions of pulp chamber and foramina. The main histologic changes were severe disturbances in the calcification process and the vascular distribution. There were also karyolysis of cell nuclei, diminution of blood and nutrient vessels and resorption of periodontal tissue, especially that of alveolar bone. All these changes were progressive. The inflammatory degenerative, and destructive changes in the rat molars after

after hypophysectomy resembled the symptoms of periodontal disease. Loss or deficiency of hypophysial function, therefore should be considered as an endogenous factor in the pathogenesis of periodontal disease.

Kluwe et al (1961) also made investigations on the effects of endocrine disturbances on the periodontal tissues, and experimented on 20 albino rats, six of which had their hypophysis irradiated with 5,000r for 565 secs, and four 10000r. Other rats had their testes or ovaries irradiated similarly. All animals showed an apathetic behaviour, and were killed on the 95th day. Inflammatory changes were observed macroscopically in all animals, and tooth mobility was marked in those whose gonads were irradiated. The most severe alterations however were seen in the periodontal membrane, the gingiva and alveolar bone, which was pronounced in the maxilla. The periodontal alterations were characterised by epithelial proliferation towards the tooth apex, formation of deep pockets, alveolar resorption and inflammatory infiltration, all being characteristic of chronic progressive marginal periodontitis in man.

Effects of growth hormone and thyroxine on hypophysectomised rat's submaxillary gland.

Dixler et al (1959) studied the salivary submaxillary glands of hypophysectomised male albino rats who were injected with growth hormone and sodium thyroxine, alone in combination. Separate, they were only partly effective in preventing hypophysectomised induced enzymatic and histologic changes and enzymatic activity. These results are comparable to those previously reported using testosterone and thyroxine in combination. Apparently the stimulating action of thyroxine on submaxillary gland function may be enhanced by the simultaneous administration of either testosterone, or growth hormone both of which are deficient in the hypophysectomised animal.

OTHER SYNDROMES.

Froehlich's Syndrome (adiposogenital pituitarism) and, Progeria (Hutchinson-Gilford Syndrome), are syndromes which seem to have some connection with pituitary gland dysfunction although their exact aetiology remain unknown.

PROHLICH'S SYNDROME (adiposogenital pituitarism, dystrophic adiposo-genitalis)

Prohlich's first patient reported in (1901) a male, was normal till twelve years of age, then developed a pituitary tumour. Rapid gain in weight followed, with feminised distribution of adiposity accentuated in pectorial abdominal thigh and mons veneris regions. Skeletal growth ceased. Genitalia were small and remained so. Associated with these endocrine changes were headache and impaired vision produced by pressure from the tumour, Braeb (1939).

Lisser and Liscanillo (1962) state that over the years, it has been common practice to label most fat children with or without evidence of sexual retardation examples of Prohlich's Syndrome or "adiposogenital dystrophy" even though most are not short but actually large for their age. It seems wiser, they state, to reserve the diagnosis of Prohlich's syndrome for patients who have evidence of pituitary tumour, usually a craniopharyngioma. However follow-up studies into manhood of boys without intracranial lesions but with the clinical picture of adiposogenital dystrophy have shown a definite incidence of adult hypogonadism, Johnson (1957). This conservative suggestion seems a good one. For the usual types of obesity in young people a concept of deranged metabolic centres near the tuber cinereum in the hypothalamus has come into vogue. Excess urinary excretion of 17-ketogenic steroids has been noted in these children Cohen (1958), and it becomes normal after weight reduction, suggesting that hypopituitarism is produced by overnutrition, in very obese individuals who do not eat excessively, it is reasonable to suppose that involvement of the hypothalamus is responsible for the obesity.

The disease generally starts in infancy, but the cause of the abnormal obesity may not be properly diagnosed until the lack of primary and secondary sex development is apparent; therefore it should not be confused with prepubertal obesity of childhood, Thoma and Goldman (1960), or to fat children whose obesity is simply due to overeating and lack of exercise, Conybeare and Mann (1952). When starting in infancy, decreased stature or even dwarfism may result due to a depressant effect on the acidophil cells of the

of the anterior lobe, but according to Englebach (1932) a tumour of the acidophil cells may result in a slight increase of stature above normal. These two types of tumours have been discovered in autopsy or operation according to Muir (1931) either an adenoma or tumour overlying the pituitary and compressing it.

#### Cranio-facial changes.

The facies are those of a fat boy or girl with round rosy cheeks. The boys have smooth skin without hair on the face or lip.

#### Dental changes.

Thoms and Goldman (1960) report that in eighteen of 21 cases, the eruption of the deciduous teeth occurred before the ninth month, three after the ninth month; eighteen of 29 cases showed normal epiphyseal union of centres; six had advanced and five slightly retarded osseous development. The teeth are of small size only in those cases with early onset, and in cases where there is skeletal overgrowth they may become overspaced especially in the anterior part of the jaws. Englebach (1932) and Beck (1932), have called attention to broad and malformed teeth, and mispaced incisors in dystrophic adiposogenitalis.

Rosch (1958) remarks that the dental status of patients with this disease appears to be better than average, and cites two cases to support it.

HUTCHINSON-GILFORD SYNDROME (Progeria).

The Hutchinson-Gilford Syndrome is an extremely rare condition affecting children, characterised by both dwarfism and premature senility.

Whilst Thoms and Goldman (1960) remark that it probably has a similar aetiological background as Simmonds disease and considers the two conditions together, an endocrine connection has not been established and as Lissor and Escanilla (1962) state does not seem likely. It certainly was thought to be associated with hypopituitarism in the young, Schour and Massler (1943). Thompson and Porfar (1950) suggest that dysfunction of the eosinophil cells of the anterior lobe of the pituitary is the underlying lesion, at the end of their review of the literature on the subject. They base this on its similarity to Simmond's Disease, and its marked contrast to acromegaly, and radiographic changes in the sella turcica.

However the opinion expressed by Lissor and Escanilla (1962) stated above is what is generally accepted today. This followed the investigations of Sheehan and Summers (1949) who say that only two autopsies have been performed with this disease; the pituitary glands were not significantly abnormal to the naked eye and histological examinations were not made, and that it is not due to hypopituitarism. However in view of its similarity to other pituitary disorder, it is thought well to include it in this review.

The first case of Progeria to be described in medical literature was that by Hutchinson (1886) under the title of "absence of hair and Mammary glands". Later Gilford recognised the condition as a clinical entity and described a case of his own and introduced the name "Progeria" (1897). There has been a tendency to use this term loosely but Crooke (1948) rightly said it should be reserved for the original specific syndrome. The rarity of the condition is seen in that Thompson and Porfar (1950) described what they felt was the nineteenth typical case. They said approximately as many atypical cases have also been described. They remark that the clinical picture of progeria is so clear cut, they did not feel justified in including these variants in it.

### Clinical Features.

Thompson and Forfar (1950) report as follows;

Conditions at birth was normal, there being no apparent hereditary or familial factor involved, failure to gain weight in the second year, and loss of hair, sex incidence is equal, dwarfism develops. In the cases presented in the literature the average weight reached by the eighteenth year was 36lb and height 46". Average age of death was 16½ years in seven cases, the oldest recorded age surviving to 26 years, Manschot (1940). Short clavicles, pyriform shaped thorax, prominent abdomen are usual. Arteriosclerotic changes occur as early as five years, and coronary occlusion has occurred as early as 7½ years. Death occurs usually from this of recurrent infections. Poorly developed muscles and arthritis as early as six years are also often present. The intellect is normal or above normal.

Radiographically; thinning and some decalcification of the shafts of bones with poorly developed mandible with crowded abnormally developed teeth, and short clavicle were observed. Thompson and Forfar (1950).

### Cranio-facial Development.

Facial features are similar in all cases producing the hydrocephalic look due to the smallness of the face, and prominence of the eyes to reduction of the size of the orbital cavities. Prominent scalp veins, late closure of the fontanelles, baldness and absence of eyebrows and eyelashes and an atrophic inelastic state of the skin are all marked. Thompson and Forfar (1950).

### Dental Development.

Thompson and Forfar (1950) gives excellent details of dental changes. They state that the primary dentition is delayed, there is a high palate and micrognathia involving the lower jaw always occurs with crowding and irregularity of the teeth, especially the incisors. Some of the teeth may be absent, abnormally developed teeth, poorly developed mandible with decalcification.

Keith (1913) in describing a typical progerian skull, recorded a case in which all lateral incisors, and upper third molars were absent and upper canines, and all lower bicuspids were unerupted.

### Treatment and Prognosis.

Lisser and Escamilla (1962) report that treatment has been ineffectual and prognosis poor. Thompson and Forfar (1950) state that

several forms of hormonal treatment has been attempted without avail, also short wave diathermy, and irradiation without success.



Fig. 11

Progeria. Photographs 1 and 2 show a boy of 15½ yrs. of age; height 3' 7"; died at age 17 yrs. of sudden heart failure. Note typical progeric faces and premature senility. Photograph 3 shows a boy of 17 years; height 3'6" which is normal for a 6 yr. old boy. Note old facies, greying hair, absence of eyebrows, senile wasting of left hand and fingers.

Lisser and Escamilla (1962).

## DISORDERS OF THE POSTERIOR PITUITARY GLAND.

### DIABETES INSIPIDUS. (Pituitary polyuria or Posterior lobe hypofunction.)

This rare disease is the one most commonly associated with posterior pituitary disorder. The cardinal symptoms are a greatly increased thirst and polyuria. The urine is of low specific gravity and sugar free. Disturbances of the posterior lobe, stalk, or hypothalamic centres, by trauma, surgical injury, tumour, or scarring from a chronic inflammation may be responsible. Also it may be due to familial idiopathic causes. The fundamental physiological change is diminished production of antidiuretic substance by the hypothalamic centres and the posterior lobe, so that the distal convoluted tubules of the kidneys lose their ability to concentrate urine. It also occurs in some 76% of cases of Hand-Schuller-Christian Disease, Thoma and Goldsman (1960).

In addition to the symptoms mentioned, the following clinical signs are to be seen:

- 1) Anorexia and emaciation in prolonged cases.
- 2) Growth of children may be retarded, (involving the dental structures)
- 3) Tendency to dryness of the skin.
- 4) Tendency to lowered body temperature.

Urinary analysis differentiates it from diabetes mellitus (glycosuria and polyuria of hyperparathyroidism (hypercalcaemia, and positive Sulzowitch Test), Lissner and Escanilla (1962).

#### Changes in oral cavity.

Very little has been reported as to this. Any changes that would occur would be due to the dehydration, if inadequate amounts of water are not available to the patient, when localised damage is done. Selye, (1949).

Nieder (1958) states that in diabetes insipidus the oral mucous membrane is bright red with parodontitis and parodontosis.

Zauscher (1958) remarks that in untreated cases of diabetes insipidus the mouth is dry, and a small volume of saliva is secreted. For this reason many such patients may exhibit evidence of rampant caries.

Treatment.

Posterior pituitary powder, as snuff is the most convenient and least expensive form of treatment in dosage of  $\frac{1}{2}$  grain, and may be necessary three or four times daily. Vasopressin administered hypodermically is also effective. Buccal tablets (80-150mg) of posterior pituitary powder have also been reported successful. Prognosis is good usually. Lissner and Escarilla (1962).