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THE PINEAL BODY
(Epiphysis cerebri)

The pineal body is a small round gland attached to the roof of the third ventricle near the junction to the midbrain. Its function is not accurately known yet, and its endocrine connection is doubtful. However, it has been suggested that the pathogenesis of pineal tumours would be either;

1. Internal secretion of a hormone. This follows the fact that the most prominent manifestations of pineal tumours are precocity, excessive sexual development and growth, it being tempting to postulate a pineal hormone.
2. Influence upon the hypophysis of an enlarged pineal tumour, may account for these changes. Because of its proximity to the hypophysis the tumour may cause pressure on it, causing either stimulation or depression of the pituitary hormone.
3. Interference with the brain centres, with which it is also in close proximity Selye (1949).

Pineal tumours, which can have a very profound effect on the body can be either cholesteatomas, liioneuromas, or teratomas (pinealomas). These tumours are extremely rare and occur most frequently in males and can occur at any age, but only prepubertal children do they express sexual and somatic over-development. Selye (1949).

This premature sexual development or macrogenitosomia praecox or Pollizzi's syndrome is the most striking clinical sign and may be very pronounced. It is somewhat similar to that found with testicular and adrenocortical neoplasms, and hypergonadism. Selye (1949), Schour and Massler (1943), Muir (1951).

Oral changes in cases of pineal tumour.

Lissor and Escanilla (1962) comment that a child of four years with a pineal tumour may have a bone age of twelve years, and is considerably taller than others their age.

Changes in the oral cavity therefore would be seen in persons in whom the pinealoma occurred at an early age, and would correspond to the general precocious somatic development of the body. Premature eruption of the teeth, and maturation of the bones of the oral region would be expected.

Experimental.

Experimental work on the Pineal Body has in the main been unsatisfactory, but Hountree (1935-1938) found that following continued injections of pineal extract in rats, the successive generations showed a retardation of the growth of the body, but an acceleration of somatic differentiation, and of the onset of adolescence. These changes appeared in the third generation, and later the result was dwarfism and sexual precocity. These results are of interest in relation to those obtained with Thyous extracts, as in both cases there was an intensification of the results in successive generations. So far as bodily growth however is concerned, the effects are of opposite kinds. Experimental removal of the pineal has as yet given no definite information.

THE THYROID GLAND.INTRODUCTORY.

The thyroid gland, whilst under the control of the anterior lobe of the pituitary, may nevertheless be considered as the "pacemaker" for the individual's mental, physical, and metabolic activities, Hawker (1950).

The normal thyroid consists of two lateral lobes each about 5cm long and 2cm wide connected by an isthmus about 1cm. wide which crosses ventral to the second and third tracheal rings. It is estimated that the weight of the normal thyroid in the adult is between 20 and 30 gms in persons residing near the sea shore and between 36 and 50 gms in persons living inland, Hawker (1950). The gland is large in youth, women, and the well nourished, and temporarily enlarges during menstruation and pregnancy, Cunningham (1947).

It is developed from the median ventral diverticulum of the pharyngeal floor and from two lateral primordia which are identified with the ultimobranchial bodies. Cunningham (1947).

The primary functions of the normal thyroid gland are:

- 1) the collection of inorganic iodide from the blood and its storage in the thyroid cell,
- 2) the synthesis of diiodothyronine and thyroxine,
- 3) the storage of thyroid hormone,
- 4) the secretion of thyroid hormone into the blood stream in accordance with physiologic needs. Gardner, Breen and Lazarin (1963)

Histologically.

The structural unit of the thyroid is the follicle (alveolus or acinus) which is round or oval space lined with a single layer of cuboidal epithelium. These vesicles are filled with colloid, the amount of which varies with the physiological condition of the gland, which consists of a protein-iodine complex, thyroglobulin, tyrosine, mono- and di-iodothyronines, thyroxine and a small amount of triiodothyronine, Spence (1961). Two of these components are naturally occurring hormones of the thyroid gland; triiodo-L-thyronine (3:5:3':5') tetraiodothyronine isolated by Harrington and Walter

(1930), and 3:5:3':- laevo-triiodothyronine identified by Gross and Pitt-Rivers (1932). Iodine is taken up in the blood stream and concentrated in the gland, acted on by an enzyme, combines with tyrosine, and oxidises to form thyroxine. The proportion of thyroxine to triiodothyronine is about 9:1. They are released from thyroglobulin by the action of thyroid and escape into the blood stream. Several synthetic thyroid hormones have been prepared and used in treatment, Spence (1961). Both thyroxine and triiodothyronine can be taken effectively orally. Recent development with radioactive iodine in the study of thyroxine synthesis, and the action of goitrogenic compounds have thrown much more light on the function of the glands in recent times.

THYROID HORMONES.

Thyroxine: was discovered and obtained from the gland by Kendall (1916) and named by him. Harrington and Salter (1930) first isolated it in its pure form as 3:5:3':5': tetraiodothyronine.

Spence (1961) states that the two fundamental actions of thyroxine are;

1. promotion of growth in the young animal,
2. the stimulation of metabolism.

The hormones also controls its own secretion by depressing the output of the pituitary thyrotrophic hormone, when the thyroxine blood level reaches a certain figure.

Growth: Deficiency of thyroxine in the young growing animal causes stunting of growth due to retardation of osseous development. The appearance of ossification nuclei is delayed, and instead of proceeding from one centre in the epiphyses as normally, it arises from multiple foci; union of the epiphyses is also delayed. Excess of the hormone causes hypertrophy of the heart, liver, spleen, kidneys, pancreas, adrenals, gonads, and lymphatic tissue. Barker (1950) states it has to do with growth of hair, teeth, skin, nails and bone.

General metabolism: The relation of the thyroid to basal metabolism

was first demonstrated by Magnus Levy (1895). Thyroxine stimulates both exogenous and endogenous protein metabolism and in excess causes a negative nitrogen balance. Thorn (1936). Excessive amounts of thyroxine causes mobilisation of glucose in the liver and thus a reduction of liver glycogen, and increased utilisation of glucose by the tissues. Marine (1935) states that depletion of liver glycogen is secondary to increased utilisation of glucose by the tissues. It indirectly causes loss of fat through the expenditure of energy and probably also stimulates fat metabolism. It depresses the level of blood cholesterol. In excess it increases the excretion of calcium and phosphorus in urine and stools probably by lowering the renal threshold for calcium and thus reduces the level of calcium and phosphorus in the plasma, Robertson (1942).

Water Balance: Thyroxine increases the renal excretion of water and salts both in normal and myxedematous subjects, Byron (1934). The increased production of urea due to increased protein metabolism may be also partly responsible for the diuresis.

Cardiovascular system: Thyroxine increases the rate of the heart-beat and the cardiac output by both direct action on the heart, and through the stimulation of metabolism.

Other Systems: The hormone stimulates mental processes, vasomotor activity, and peristalsis, and maintains the normal texture of the skin and growth of hair. It stimulates the formation of the erythrocytes, but its effect on the leucocytes is variable.

Triiodothyronine

This second hormone of the thyroid gland is similar to thyroxine in its effects, being five times more potent in preventing thiouracil goitre and in promoting the growth of thyroidectomized rats, Gross and Pitt-Rivers, (1933) and three times more potent in the treatment of human myxedema. Its action is more rapid and less prolonged than thyroxine. Spence (1961).

DISEASES OF THE THYROID GLAND. Selye (1949) gives a general classification of the diseases, of the thyroid as follows;

1. Malformation, aplasia, hypoplasia, hyperplasia.
2. Inflammations, acute, and chronic thyroiditis.
3. Simple goitre, diffuse and nodular.
4. Hypothyroidism leading to an excess of thyroid secretion.
5. Hypothyroidism leading to a deficiency of thyroid secretion.
6. Tumours of the thyroid.

Goitre simply means thyroid enlargement, and has been classified in many ways. Goitres can cause both hyper and hypothyroidism, but are not the only cause of these conditions.

The American Association for the Study of Goitre has adopted the following terminology;

1. Non-toxic goitre, diffuse (endemic and adolescent) and nodular adenomatous or colloid). This does not produce hyper or hypothyroidism.
2. Toxic goitre, diffuse (Grave's Disease, primary hyperthyroidism) or nodular (toxic adenoma, secondary hyperthyroidism).
3. Malignant goitre.
4. Inflammatory disease.

Selye (1949) states that the functional classification is the best from the endocrinologist's point of view and suggests simply;

1. Simple goitres leading to no endocrine symptoms.
2. Hypothyroid goitres, leading to a deficient thyroid secretion.
3. Hyperthyroid goitres, leading to excess thyroid secretion.

It is noticed that Lissner and Eneasilla (1962) used a somewhat similar general classification as Selye (1949).

Obviously not all these conditions will have an oral bearing, and it is intended to consider hyperthyroidism, hypothyroidism and make brief reference to simple endemic or puberty goitre, and lingual goitre and thyroiditis.

HYPER-THYROIDISM. (Exophthalmic goitre, thyrotoxicosis, Grave's disease, Parry's Disease, and toxic adenomatous goitre or Plummer's Disease).

HYPERTHYROIDISM. (Exophthalmic goitre, thyrotoxicosis, Grave's Disease, and Plummer's toxic adenomatous goitre.)

Caleb Parry (1786), Flajani of Italy (1802), Graves of England (1835), and Van Basedow of Germany (1840), each described exophthalmic goitre. Hyperthyroidism is due to an excess of thyroid hormone circulating in the body, and has been subdivided into two main types by Dooyhby and Plummer (1936).

1. Exophthalmic goitre, characterised by diffuse hyperplasia of the thyroid gland and by eye signs,
2. Toxic adenoma, in which hyperfunction originates from a benign tumour of the gland.

Selye (1949) adds Hyperthyroidism without goitre (functional hyperactivity, 10% of cases.

Lisser and Escamilla (1962) remark that over activity of the thyroid is seen frequently in clinical practice. Incidence in females is four times more than in males, and it is rather rare in children, extremely so in boys (nearly always of the hyperplastic type). It may be congenital. Selye (1959) reports that it is four times more common in females than in males in areas where it is not endemic (non-goitre areas) and in ratio 4:3 in goitre areas, such as Michigan, USA. It profoundly affects the metabolism of the body. Bilateral exophthalmos is a striking feature of hyperplastic goitre, and therefore designated exophthalmic goitre. The exophthalmos is now thought consequent to an excess of thyrotrophic hormone (TSH) or perhaps to a separate specific pituitary hormone not yet known, pregnancy, menstruation, trauma.

The pathological picture consists of uniform hyperplasia or scattered areas of hyperplasia in association with multiple adenomas (toxic adenomatous goitre). This latter (or Plummer's Disease) occurs more frequently in older patients (over 40) and nodular goitre may have been present for many years before onset of hyperthyroidism. Selye (1949) adds that the main difference between these two main types of hyperthyroidism is that in Plummer's adenoma exophthalmos and tremor are usually absent and hypertension is common, while the thyroid enlargement antedates the signs of the disease.

Malignant Exophthalmos; (Progressive exophthalmos) is a serious malady characterised by advancing exophthalmos, which may lead to

blindness and death, and is usually associated with hypothyroidism of Grave's Disease, but not caused by it. The hyperthyroidism may be only mild, Lissner and Lescanilla (1962).

Clinical Features of Hyperthyroidism:

The chief are nervousness (episodes of extreme excitability, emotional instability), shakiness or tremor, cardiac palpitation (heart rate up to 200), and shortness of breath, and other signs of congestive heart failure, unpleasant feeling of warmth, loss of weight in spite of excellent appetite, fatigue, gastrointestinal symptoms, polyphagia and polydipsia, goitre, exophthalmos, diminished menstruation, rapid growth in children, abdominal pain occasionally; occasional enlargement of the spleen and thymus, pretibial myxedema, clubbing of fingers and toes and undermined nails (Plummer's Nails). Lissner and Lescanilla (1962). The most serious complication that arises at times is thyroid crisis if untreated, Selye (1949).

Laboratory and Radiographic Findings:

Laboratory tests show an elevated basal metabolic rate from +30 to +100%, (normal is -10% to +10%), serum protein-bound iodine level is increased, and there is a rapid rise in the uptake of radioactive iodine, serum calcium may be slightly elevated.

Urinalysis, shows a mild glycosuria and hypercalcaemia, Aub et al (1929).

Radiographic examination may show thyrotoxic osteoporosis (involving the ribs and long bones) and an advanced bone age in children. Leake (1955) gives an interesting discussion of the osteoporosis associated with thyrotoxicosis.

Cranio-facial Changes:

Thomson and Goldman (1960) comments that the facial expression is one of excitement with wide-eyed staring. The development of exophthalmic goitre causes a protrusion of the eyeballs with exposure of the sclera. The face is usually small and very narrow with cheek bones and other bones, such as the clavicles protruding.

Dental Changes.

The thyroid osteoporosis of bones may affect in extreme cases the alveolar portion of the jaws causing atrophy. Thoma and Goldman (1960-). Also the ossification of the epiphysis, which occurs several years earlier in the hyperthyroid child than the normal child. Velti (1939) has been described in a girl aged five years whose wrists showed a bone age of ten years. There was an extraordinary development of the dentition also. The deciduous teeth started to be shed, when she was three and a half years old and at five years of age her dentition corresponded to that of a child of nine years. Hosh (1958) refers to a child of four and a half years with diffuse goitre and hyperthyroidism who had early eruption of the teeth. The deciduous teeth were erupted at five months. There was severe caries of the deciduous teeth, which were discoloured and showed a growth diastema. Thoma and Goldman (1960) state that in hyperthyroidism the teeth may erupt early and the dentition likely to change prematurely. The enamel of the teeth is often bluish white in colour. Middleburgh (1939) showed that in infancy there may be early eruption of the permanent teeth.

Schaffer (1957) reports a case where periapical rarefaction occurred in a patient with Grave's Disease. The areas of bone loss filled in completely when the patient had a subtotal thyroidectomy. An interesting feature of the case is that radiographic records, intact over a period of sixteen years disclosed the first evidence of periapical rarefaction more than two years before the clinical picture of thyrotoxicosis appeared. There was no evidence of any pulpal disease. These findings would show some correlation with the results of Goldman (1943), experimenting with guinea pigs, which were a marked osteoporosis especially of the spongiosa with no evidence of repair by osteoblastic activity as you get in hyperparathyroidism.

Gardner et al (1963) state in their review of the current literature, that children with hyperthyroidism exhibit a more rapid than normal development of the calcium portion of the body. The dental development is usually in keeping with the epiphyseal age of these patients which is also advanced. It is reported that

morphologically the teeth of hypothyroids are no different to normal teeth, that they have a bluish tinge, are firm, and graceful, that they may be thin and transparent, may be intensely decalcified and that there may be exaggerated growth of the crowns as compared with normal teeth. The developmental changes occur if the onset of the hyperthyroidism occurs before the dentition is fully formed. Caries incidence is high in the deciduous teeth and a growth diastema is usual, which corresponds to Rensch's observations (1958). Early eruption of the permanent dentition occurs as well as with the deciduous dentition. It is reported that there is a tendency towards early and extensive caries, consistent with alveolar resorption.

The maxilla is thin and more dolicho than usual, and exhibits increased radiolucency with some osteoporosis of the supporting bone of the teeth with a resultant fine trabecular pattern. Experimental thyroxine injections in animals show that osteoporosis, periodontosis, and alveolar resorption occur. There is increased vascularity of the alveolar-dental periosteum and increased osteoclastic activity along the lamina dura. These findings may be accounted for in part by the increased body metabolism, and the increased calcium secretion by the body in hyperthyroidism.

Schour and Hassler (1942), remark that paradontosis (periodontosis) has been said to be associated with hyperthyroidism but this has not been substantiated in the few cases seen by them. However, three of the six patients Rensch, (1958), studied showed advanced periodontal disease. The six had oral neglect, and five had a definite caries susceptibility. Hutton (1936), comments that oral sepsis is often associated with toxic goitre.

Gardner et al (1963), state that local infection appears to have some injurious effect on the thyroid gland and specific cases have been reported where hyperactive thyroid glands have been aggravated by oral infections and relieved by the elimination of the infection. Infected tonsils may also cause this. But these factors cannot be considered as causative of hyperthyroidism.

Dental Treatment of Hyperthyroid Patients;

Thoma and Goldman (1960) remark that hypothyroid patients make very poor dental patients, because of their increased nervousness, emotional instability, tachycardia and hypertension and sensitivity to adrenalin. Serious and even fatal results may follow dental extractions in unprepared hyperthyroid patients.

Ustrander (1958) adds that patients taking thyroid substances show a low tolerance for opiates, which should be avoided in surgery. He also states that thiouracil treated patients occasionally present a peritonitis and aggranulocytosis. He concludes that any hyperthyroid patient whether under treatment or not, is a poor risk for extensive dental treatment and the matter should be discussed with the patient's physician.

Hyperthyroid patients should receive proper treatment before dental treatment is done, as a thyroid crisis may be precipitated otherwise. Drugs dependent on the liver for detoxication should be avoided due to the diminished liver function in hyperthyroidism. Atropine is definitely contraindicated because of its vagal inhibitory effects, Archer (1961), Thoma (1963).

Gardner et al (1963) remarks that general anaesthesia is advised in hyperthyroid patients, but only after medical treatment has been instituted, in dental surgery, as there is less psychic trauma, than with local anaesthesia. Adrenalin should be avoided if local anaesthesia is used. Dental treatment, if necessary, they advise, should be simple in character, with adequate premedication, and of short duration.

Treatment of Hyperthyroidism;

Lissac and Escamilla (1962) state the following;

- 1) Surgical subtotal thyroidectomy gives the best results in most cases, in patients premedicated with iodine and antithyroid drugs.
- 2) Antithyroid drugs used alone when the goitre is small and surgery contraindicated. Iodine, potassium perchlorate, propylthiouracil, methimazole, iodothiouracil, carbimazole, (which is probably the best drug to use), Cope (1952), Garrod (1961).
- 3) Radioactive Iodine (131) taken up by the gland, thus treating

by radiation from within, was first introduced in (1942) and offers the safest form of treatment in older patients. It avoids the toxic reactions of antithyroid drugs and the disastrous surgical hazards of laryngeal palsy and hypothyroidism, and laryngeal oedema causing tracheal obstruction. There are some risks associated with it, so that it should be given only exceptionally in patients under 45 years, which is current policy in Great Britain, Garrod (1961). Also Sheline and Miller (1959), Cassidy and Astwood (1955) and Debit et al (1961).

4. X-ray treatment of thyroid, should be confined to hyperplastic Graves Disease.

5) Adjuncts; (a) Sedatives

(b) Potassium chloride for muscular weakness,

(c) Calcium, phosphorus, Vitamin D,

(d) High caloric diet,

6) Thyroid Crisis. Heavy sedation, iodine, antithyroid drugs, digitalisation, ACTH, hydrocortisone, etc.

7) Malignant Exophthalmos. Dessicated thyroid, increased to tolerance to inhibit thyrotrophic hormone production. Some report that, triiodothyronine is superior. ACTH and steroid therapy has been successful, and pituitary irradiation proved successful by some. Thyroidectomy is to be avoided.

Prognosis. Is usually good if correct treatment is given before permanent circulatory damage has been done. Death will ensue if untreated. Lissner and Escamilla (1962).

EXPERIMENTAL HYPERTHYROIDISM.

Schour and Massler (1941) point out that the effect of experimental hyperthyroidism, whether due to thyroid extract given orally by injection, is to raise the metabolic rate, which in turn causes an increase in rate of cellular differentiation, loss of weight, rapid heart beat, flushing, and increased nitrogen excretion.

Hellanby as early as (1923) found that adding dried thyroid to vitamin-deficient diets, increases the development of rickets in experimental animals.

Aub et al (1929) found that in exophthalmic goitre the excretion of calcium is greatly increased, and in one severe case, it was eight times the normal without being accompanied with hypercalcaemia. This and other findings (eg increased radiolucency on X-rays of hyperthyroid patients) suggest that bone resorption is occurring. This was investigated further at a much later date. Bauer, Aub, and Albright (1929) found that osteoporosis produced by resorption of both spongy and cortical bone was associated with hyperthyroidism.

Zavadovsky (1929) in his studies on the effects of thyroid on the salivary action of dogs, found that the feeding of thyroid to dogs and guinea pigs caused a loss of hair, giving them a scraggly appearance, but there was no apparent blanching of colour.

Boskins (1929-28) injected 0.1mg of acetyl thyroxine, a derivative of thyroxine which does not affect the metabolic rate of mammals as does thyroxine, into new born rats. It caused the rats to go through changes of form normal for the first twenty five days of life in a period of fifteen days. It also caused changes in the proportions of the skull, and the development of the hair, eyes, auricles and feet. She also noted that there was a hastening of the eruption of the incisors, and that enamel formation was accelerated but was normal in its structure.

Smith and McLean (1938) made chemical analysis of the bones of hyperthyroid rats and showed that there was no evidence of

failure of calcification, growing of older rats with diets adequate in calcium. They found however, that there was cessation or marked retardation of growth at the epiphyseal junctions of the femur and tibia of rats between 4.5 and eight months old.

Karnofsky and Crenkite (1939) showed that injections of thyroxine in sufficiently large doses in new born rats resulted in a precocious eruption of the incisors three days later (normally the teeth erupt in about ten days.)

Hertzberg and Schour (1941), experimenting on older rats found that eruption of the continuously erupting incisor is accelerated.

Ziskin and Applebain (1947) injected thyrotrophic hormone (TSH) into Rhesus monkeys and found that all the animals showed some increase in the rate of dentine deposition. The rate of increase varied from 10% to 60% in different animals and in different areas of dentine in the same animal. Marx, Simpson, and Evans (1942) found that thyroxine augments the cellular proliferation that is normally associated with growth hormone replacement therapy so acting in a synergistic way in hypophysectomized animals.

Goldman (1943) in a detailed and interesting survey as to the effect of thyroxine on the jaws and supporting structures of the teeth fed 32 guinea pigs a measured amount for six to 100 days. Their general findings were as follows:

1. The animals lost weight and their hair became thin, giving them a scraggly appearance. The animals' nails degenerated and in many instances were lost.
2. Radiographic findings; on comparison with the controls, there was seen an osteoporosis of the bony structure of the entire skeleton especially of the skull, femur and tibia. The size and shape of the incisor teeth are similar to those of the controls, but on close observation the outlines of the pulp chambers in the experimental animals appear less clear-cut.
3. Histopathologic findings; Osteoporosis of the bones is striking and osteoclasts are very numerous. Osteoblastic activity is marked and the marrow is slightly fibrous, but there

are many areas of haemopoiesis. There was a marked resorptive process and osteoblastic activity seen in the mandible. There were definite changes in the ribs and tibia and femurs.

The dentition; The incisors showed changes which varied in different parts of the tooth. The odontoblasts lose their columnar shape, becoming spherical, and are not uniformly arranged. The nuclei are pyknotic and indistinct; atrophy and disorientation are characteristic. Two grades of dentine formation are observed; one type more regularly formed than the other, which was slightly stained with few and irregular tubules and is formed in wavy bands which show light and dark striations. The formation of trabeculae deficiency, is found and is the result of the loss of continuity of the odontoblastic layer. In areas where the odontoblasts are still functioning, dentine continues to be formed, but where the odontoblasts had become atrophic dentine production of spicules with bay-like recessions between, in which remnants of odontoblasts and blood vessels are found. These disturbances in the dentine was like osteodentine. The changes in the bone differentiated from those found in vitamin A, and C, deficiencies, hyperparathyroidism and low-calcium experiments, and magnesium deficiency.

Goldman in a subsequent report, following experiments on guinea pigs which received supplemental vitamin C, made the following comments; The teeth especially the molars, became very loose. The periodontal membrane showed increase vascularity and evidence of diapedesis and it was noticeable that more blood vessels extended from the periodontal membrane into the marrow spaces. The walls of the channels in the bone through which the vessels pass, were also affected by resorptive activity. In the case of the molar teeth, there was more active osteoclastic type of resorption of the alveolar sockets than that seen in the incisors and the resorption of the alveolar rest between the teeth. It is of interest to note that while this action was going on everywhere, there was no evidence of repair by osteoblastic activity, which is a feature of hyperparathyroidism. (reported in Thoma and Goldman (1960)

Simpson, Asling and Evans (1950) have shown that thyroxine primarily acts to accelerate skeletal maturation and that it has

no growth promoting effect. These conclusions were based on endochondral growth occurring within the epiphyseal plate of long bones. Roy et al (1950) also found that the administration of thyroxine to hypophysectomised rats prevented the arrest of endochondral ossification which normally occurs in the untreated hypophysectomised animals. However, the relationship of the thyroid to non-endochondral osteogenesis has not been demonstrated. Bayetta et al (1957) found that thyroid feeding of rats accentuated the osteoporosis of alveolar bone induced by tryptophane deficiency.

Dental Caries.

Much research has been done on the relationship of dental caries to thyroid function, and also the part played by the major salivary glands in it. The experiments of Muhler and Shafer (1954, 1955), and Bixler, Muhler and Shafer (1956), and Bixler and Muhler (1957), and Muhler and Shafer (1958, 1959, 1960), and Shafer, Clark Bixler, and Muhler (1958, 1959) indicate a relationship between the secretory activity of the thyroid gland and resistance to dental caries. Changes in the structure of the salivary glands and in their amount of secretion and its viscosity were also consistently observed. The cariogenicity of the diet of rats was decreased by the addition of desiccated thyroid. Diminished salivary flow and increased salivary viscosity in hypothyroid rats was restored to normal by feeding them with sodium thyroxine. A full account of these and addition experiments by Haldi, Hynn and Law (1961, 1962) and others is recorded under "Experimental hypothyroidism".

Periodontium.

Rosenburg, Goldman and Garber (1961) studied the effects of thyroid dysfunction on the periodontium of New Zealand rabbits. Thyrotoxicosis was induced by administering daily injections of thyroxine (0.25mg/kg body weight). Gross findings in the thyrotoxic group include loss of weight, nervousness and a red smooth tongue. Histologic findings were a relatively unaltered gingivae; a cellular well-organised, slightly thickened periodontal ligament; and a bone picture of relative activity. Very much more profound changes in the other myxoedematous group were

studied. (see Experimental hypothyroidism).

Shaw (1960) found in his experiments on 60 rats, that both hyperthyroidism and hypothyroidism have no effect on tooth migration.

Burston and Shafer (1961) used a method for artificially expanding the premaxillary suture of the rat to investigate the effects of thyroid dysfunction on osteogenesis. Three groups - hypothyroid, hyperthyroid, and control were compared as to sutural activity. Whilst variation was evident in the degree of separation of the suture, no consistent difference among the groups were found. No differences were noted in the orientation of the collagen fibres or the vascularity of the connective tissue between the experimental and control groups. Propylthiouracil treated, animals showed more profound tissue reaction at the site of suture separation than either control or hyperthyroid groups, (see Experimental hypothyroidism). These results have to be compared with those of Ray et al (1950), Marx, Simpson and Evans (1942) and since long-bone growth has a chondrogenic component that is not present in sutural growth, it is not surprising that the effects of hyperthyroidism and hypothyroidism on the growth of long bones is not the same as the effects on sutural growth, Burston and Shafer (1961).



Fig. 4a

Fig. 4b

Fig. 12

Exophthalmic goitre, in man aged 27. Duration 16 months; BMR, plus 85%; sleeping pulse rate, 110; radioiodine uptake, 72% in 24hrs. Note exophthalmos and enlarged thyroid gland. Photograph 2 is same patient after 4 months treatment with 6.4 millicuries of I^{131} . Pulse is normal and BMR is minus 10%.

Lisser and Escamilla (1962).



Fig. 13

Hyperthyroidism, bone loss. Schaffer (1957).



FIG. 49.



FIG. 50.

Hyperthyroidism in infancy and premature eruption of teeth. Female. Age: 4 years and 11 months. Prematurely born at 7 months and weighed 3½ lbs. Other family history normal. Never ill but sleeps poorly and very nervous. Photograph shows exophthalmos and enlarged thyroid gland. Models show $\frac{61}{21} \frac{16}{12}$ erupted or in process of eruption. Some of the deciduous teeth are carious. Thyroidectomy subsequently performed.

Fig. 14

Hyperthyroidism, in infancy and premature eruption.
Stones (1954).



Fig. 15.

Adult Myxedema, in man aged 52 yrs. Typical facial expression and fingers. Grollman and Burkitt (1959).



Fig. 16

Cretinic Dwarfism. Boy aged 17 years. Cargel index indicates a bone age of 2yrs. 8mths.

Chereskin and Langley (1956).



Fig. 17.

Cretinic dwarfism in boy aged 17 yrs. Same case as above. Radiographs show delayed eruption of the second bicuspiids, and delayed loss of deciduous teeth. Chereskin and Langley. (1956).

HYPOTHYROIDISM.

Lisser and Escamilla (1962) gives the following classification;

1. Endemic cretinism or cretinic degeneration.
2. Childhood Myxedema (congenital, infantile and juvenile types)
3. Adult hypothyroidism (Myxedema, Gull's Disease, Lisser and Escamilla syndrome of internal myxedema, primary hypothyroidism)

ENDEMIC CRETINISM.

Is a rare congenital condition limited to certain regions of the world, especially Switzerland, the Himalayas, and the Andes. The cause is thought to be due to lack of iodine in drinking water, and possibly toxins locally from soil or water bacteria. It is usually already manifest at birth and goiterous enlargement is commonly associated with it. Goitre is often seen in the parents. The clinical picture is somewhat the same as in infantile myxedema, and will be considered under that heading, but benefit is not consistent from thyroid administration. The condition is to be deaf-mutism and tendency for cretins to show a high ^{131}I uptake due to avidity of the gland for iodine, Lisser and Escamilla (1962).

CHILDHOOD MYXEDEMA.

Has been divided into;

1. Congenital type; occurs in 5-10% of cases in the US, and is due to some congenital enzymatic defect in thyroid hormone synthesis.
2. Infantile type; most cases are of this type and it occurs about twice as frequently in girls. Congenital absence of the thyroid or its atrophy may provoke the clinical picture; associated goitre is rare. Clinical manifestations resemble those of adult myxedema, but deficient growth, sometimes sexual retardation, and almost always, impaired mentality constitute important additional characteristics. The disease is not inherited as a rule, Lisser and Escamilla (1962).

3. Juvenile types; which is hypothyroidism acquired between the ages of six years and twelve years, ie before puberty, resulting in short stature and delayed bone age. If the hypothyroidism occurs after this, it is generally designated adult myxedema which will be considered.

Clinical Features.

Lisser and Escamilla (1962) list the following Symptoms and Signs for Childhood myxedema;

1. Typical myxedematous appearance, recognisable at first glance in severe cases, characterised by thick, dry rough, flakey yellow skin sometimes in folds, puffiness of features especially around eyes and lips; thick large tongue usually protruding from open drooling mouth; stupid dull appearance.
2. Dwarfism of retarded development.
3. Mental dullness and listlessness, to varying degrees.
4. Head proportionately large with delayed closure of fontanelles.
5. Sparse hair, bristly, dry and straight, Nails are brittle.
6. Saddle type nose.
7. Late eruption of teeth, and teeth irregular and decayed.
8. Short thick neck, but goitre is rare.
9. Protruding abdomen, and often umbilical hernia.
10. Relatively short extremities.
11. Retarded genital development usual, but occasionally precocious development in girls evidence by irregular and profuse menstruation.
12. Hypothermia. Patient's skin feel cold.
13. Constipation.
14. Poor Speech.
15. Nasal stuffiness and tendency to respiratory disease.

It must be understood that all degrees of severity are encountered, and only one or two symptoms may appear in mild cases.

Lurie (1938) called attention to a clinical syndrome of extreme restlessness, destructiveness, and speech disturbance which almost always indicates a state of hypothyroidism.

Thom, and Goldman (1960) state that many mild forms of hypothyroidism are aggravated in the first few years of life, by infectious disease such as chicken pox, measles. They also remark that the myxedematous enlargement encountered and is due to oedematous infiltration of the cutis caused by stellate connective tissue cells. Shafer, Hine and Levy (1963) add that it is due to an accumulation of water and protein in the tissues. Underdevelopment of the skeleton is the most reliable sign of cretinism, (infantile myxedema) and is diagnosed by means of radiographic examination of the wrist, and other joints which show similar signs. The times of appearing of the ossification centres, progressive ossification, and times of union of the epiphyses are observed. Thome and Goldman (1960) Behar and Hassler (1943) remark that in cretinism bone growth is almost completely arrested, while the soft tissues are profoundly, but relatively less affected- leading to obesity in the cretinic dwarf, but they differentiate between dwarfism in hypothyroidism and in hypopituitarism. Obesity, and mental retardation usually occurs in hypothyroidism but does not in hypopituitarism.

Changes in Oral Region.

McCullagh and Kersch (1941) state that the endocrine disorder most clearly related to dental formation and the rate of eruption of the teeth, appears to be thyroid deficiency.

Gardner et al (1963) makes the following striking comments. Hypothyroidism is perhaps the most common of the endocrine disturbances. Many cases of myxedema are mild and may go unrecognised for a long period of time. Many times it is the dentist that makes the first observation of thyroid deficiency. In Tager's study (1951) of orthodontic problems of 100 children, he showed that there were ten cases of frank endocrinopathy amongst them. Of these ten, nine were hypothyroids. Harinus (1934) remarked that in his opinion that a third of the patients seen by the orthodontist were victims of thyroid deficiency, and that thyroid therapy is only mildly helpful as the deficiency occurred during the development of the tooth and jaws. However, it appears that this figure of one third is too high.

Growth of the Jaws; Thoma and Goldman (1960) state the following;

The base of the skull is shortened which causes a retraction of the bridge of the nose which becomes extraordinarily wide, and the entire face develops a lateral rather than vertical direction, which may be due to part of delayed union of the palatal suture. There is also maxillary protrusion, which de Quervain and Vegetin (1936) state produces the effect of a "monkey face". This is accentuated by underdevelopment of the chin, due to the effect on cartilaginous development (osmentis). Non-Union of the mandible has been reported by Knaggs, (1929), and the failure of the frontal sinuses to develop was found a consistent feature by Spitzer and Quillam, (1958), who also found in some instances that the maxillary sinuses were small. They also state that the maxillary and mandibular micrognathia is impressive.

Buckman (1957) states that the malocclusion appears to be constant finding in cretinism, due to faulty patterns of growth and development. The enlarged protruding tongue often causes an open-bite which coupled with the relatively overdeveloped maxilla, and underdeveloped mandible results in varying stages of malocclusion. Shafer, Hine and Levy (1963), Stones (1954) adds that separation of the teeth with protrusion of the teeth may also result from the tongue abnormality. Schour and Massler (1943) comment that the presence of the teeth, which are less severely affected than the jaws, and their partial eruption result in an alveolar process and dentition, which although diminished in size and crowded, appear to be large only in proportion to the size of the bases of the jaws, which are small due to the arrested bone growth. The result is a protrusion and disproportionate size of the dentition which displaces the mandibular base downwards, and backwards. A cretin of chronologic age 20 but bone age of three years, may have a dentitional age of eight years, the effect of which is like putting a eight year old dentition into a three year old skull, Means (1948). Engel et al (1947) gives a detailed analysis of the cephalometric findings in hypothyroid patients. Crigley et al (1962) found

similar results as Engel et al (1941). Engel et al in (1948) reported further that ossification patterns of development were deficient in the cranium at the occipital, parietal, and to a much lesser extent, the frontal areas. The face showed a generalised retardation of growth as a result of the slowed velocity of growth of its component parts; ie maxilla, mandible, and nasal bones. The teeth are delayed in eruption but are not malformed. Hypothyroid children who have been treated regularly since early childhood, closely approach normal levels of cranio-facial development. The conclusions reached, from this study is that thyroid deficiency affects cranio-facial growth by retarding its velocity rather than by modifying its pattern.

Development of the Teeth.

Schour and Massler (1943) remark that the enamel, dentine, and cementum, appear to be normal in structure and form, but retarded in development. This delay in formation of the dentine is indicated by the incompletely developed roots and open pulp canals observed on radiographs. The effect on the growth of the teeth is much less marked than that upon the bony jaw base and alveolar process upon eruption. Engel et al (1948) supports this view. Gardner et al (1963) however, add that large maxillary central incisors and small lateral incisors have been noted in hypothyroidism. In certain individuals a common genetic background predisposes to congenitally absent teeth, both deciduous^{and}/permanent, which is in addition to the hypothyroidism. The upper lateral incisors are most often absent. Morphologic abnormalities, such as poorly formed teeth, enamel dysplasia, Marinus (1934), Wolf, (1939) Glassey (1939), Levy (1940), Escamilla (1951), and supernumerary teeth, Levin (1951), have all been reported in the literature. But Meyerhofer (1914), Schour and Massler (1943), and Buckman (1957) have not found them in observations. Structural deficiencies, especially marked in the first molars, appearing as hypoplastic areas between the cusps have been reported by Marinus (1934).

Seward (1963) states that cretinism can effect amelogenesis

and occasionally the effects are apparent in the adult dentition. He shows radiographs of an adult cretin, untreated till over one year old; the tips of the upper central and canines incisors were affected by systemic hypoplasia but the lateral incisors were unaffected. A double line of pits was seen affecting the tips of the canines and the centrals were most devoid of enamel over their incisal third.

Eruption of the Teeth.

The most striking and universal changes in the dentition of the hypothyroid child is the alteration in the eruption and exfoliation of the deciduous and permanent teeth, Resch (1958) Eruption of the deciduous teeth particularly is delayed, and as Siegert (1928) points out may not commence till the age of three years. Permanent teeth eruption is also delayed but due to retarded exfoliation of the deciduous teeth, may erupt alongside the deciduous teeth giving an appearance of a double row of teeth anteriorly. Schour and Massler (1943) state that, nevertheless eruption is less retarded than bone growth. Meyerhofer (1914) made observations on 13 cretins and found similar abnormalities.

Changes in the Periodontium:

Hutton (1936) and Escamilla (1951), report that the thyroid glands plays a basic role in gingival tissue health. The literature does not appear to show a reference of periodontal disease associated with cretinism, except for a statement that cretins are more susceptible to Vincent's Infection of the gingivae by Means (1948) and Glickman (1958), until Buckman (1957) reported the case mentioned below. However, there are many references to periodontal disease associated with myxedema Becks (1941), Rosenthal (1949), Reynolds (1933), Lewis (1935) etc; This may well be due to the fact that reported cases of cretinism fall into a lower age group when periodontal disturbances are not so common.

The gingival tissues in hypothyroidism can be normal or

pathologic, Gardner et al (1963), Brucker (1933) in his interesting treatise found that there is a greater incidence of gingivitis in the myxedematous patient, Buckman (1957) found in a 22 year old woman cretin . . . poor oral hygiene, yet 28 permanent erupted teeth with no caries.

In the five hypothyroid patients examined by Gardner et al (1963) four displayed fair to good oral hygiene, and all exhibited extensive dental restoration or were in need of it.

There has been a good deal of research on animals as to caries incidence in hypothyroidism, also on its relation to salivary flow and viscosity, particularly by Muhler and Shafer (1954-1960) and Haldi et al (1961-1962). The essence of these reports which will be discussed more fully later under, Experimental hypothyroidism is that the higher caries incidence is probably due to an accumulation of carbohydrates because of decreased washing action of the saliva and possibly the decrease in its iodide content.

ADULT MYXEDEMA (Myxedema, Gull's Disease, Escamilla-Lisser Syndrome, Primary Hypothyroidism).

This chronic disease affecting adults, occurs when hypothyroidism arises after puberty. Onset may follow from atrophy, sclerotic destruction, or idiopathic fibrosis, partial or total thyroidectomy and occasionally from prolonged large doses of iodine. Full-blown myxedema is characterised by a myxedematous thickening of the skin, subcutaneous tissues, and mucous membrane together with a slowing of all vital processes. Most characteristic, are the dramatic benefits received from desiccated thyroid, which reverses most of the abnormalities toward normal. Milder instances are much more common, and frequently go unnoticed, and a suspicious alertness to this condition is desirable. In its full form, myxedema is comparatively rare and occurs throughout the world, and is about four to seven times more frequent in women than men. Onset is usually about middle life and is slow and insidious, Lisser and Escamilla (1962). Changes in the oral region are not so profound in this type, as the dentition is fully formed before onset but there are changes in the periodontium, Gardner et al (1963). In milder formes, myxedema is quite common. Selye (1949), states that about one in every 1,500 patients administered to hospitals in America are suffering from myxedema.

Clinical Features the symptoms and signs as described by Lisser and Escamilla (1962) are;

1. Weakness and lethargy.
2. Hypothermia.
3. Dryness, roughness and pallor of skin, brittleness of nails and hair.
4. Muscular pains.
5. Constipation.
6. Circulatory symptoms, dyspnoea, bradycardia.
7. Menometrorrhagia, but occasionally amenorrhoea and sterility.
8. Ear, Nose and Throat symptoms. Chronic hoarseness prolonged

sinusitis.

9. Myxedematous appearance to varying degrees.
10. Mental lathargy, listlessness, loss of memory, slowness of speech.
11. Moderate obesity.
12. Teeth may decay rapidly, and may actually fall out.
13. Thyroid gland usually small and difficult to palpate.

Laboratory tests; (also apply to Childhood myxedema)

- 1) Basal metabolic rate depressed
- 2) Blood protein-bound iodine levels low, as is butanol-extractable iodine.
- 3) Chest X-Ray reveals large flabby atonic myxedematous heart, and fluid.
- 4) Plasma or serum cholesterol high.

Differential diagnosis from pituitary myxedema is to be noted as mentioned earlier. The pituitary shows serum cholesterol levels normal and marked disturbances in sexual function is evidence of pituitary tumour, or post-partum haemorrhage. Results of ¹³¹I uptake stimulation by TSH clarifies the distinction. It is low (7.6%) in primary hypothyroidism, average (20.8%) in normals, and high in pituitary myxedema (32.2%). Differentiation is important as treatment of pituitary myxedema with thyroid may precipitate adrenocortical crisis, Lissner and Escamilla (1962).

Dental Changes;

There is the typical myxedematous appearance of face, lips, and tongue as mentioned previously.

Hirschfield (1934), Hutton (1936) Becks (1947) described chronic periodontal disease and alveolar bone loss in association with myxedema. Lewis (1935) has made similar observations, but reports an improvement of the condition after treatment of the disease. Resch (1958) and Gardner et al (1963) refer to a study of myxedema in a Cleveland clinic with the

following results; of 38 cases with complete dental records, 26 showed little or no periodontal disturbances, twelve showed moderate or marked periodontal disturbances and eighteen had marked caries susceptibility. In his studies of adult hypothyroidism, Rosenthal (1939) discussed marginal gingivitis, lustreless enamel, about the necks of the teeth, high caries susceptibility, death of the pulp beneath shallow restorations, and failures in root canal therapy. All of these responses suggest reduced regenerative power in the pulp and periapical tissues. Obviously there is much to be determined yet as to the true bearing^{of} myxedema on the oral cavity.

Treatment of Hypothyroidism.

The treatment of congenital hypothyroidism should commence at birth, if mental damage is not to occur, as the brain doubles its size in the first year. Therefore the skeleton can withstand a much longer absence of thyroid function than the brain, thus a cretin in whom treatment is delayed till the age of three years may become almost normal in height in spite of being very defective mentally, Thompson (1951).

The hypothyroid patient responds very readily to iodine when there is active thyroid tissue present, or thyroid medication. Prophylactic treatment given to the progenitor may prevent transmission of hereditary thyroidism. The quick response to thyroid therapy is useful in forming a differential diagnosis from non-endocrine disease such as achondroplasia.

Improvement is only partial in cases of cretinic degeneration, and care in institutions as often necessary. Prophylactic provision of iodised salt in endemic areas is advisable, Lissner and Escamilla (1962).

Dessicated thyroid, Throxine, triiodothyronine are all used in the treatment of myxedema, and prognosis is generally good if started early and is faithfully continued. However, hypothyroid patients are prone to arteriosclerosis and early death. Myxedema coma may occur in untreated cases. Lissner and Escamilla (1962).

As far as the teeth are concerned, von Kutschera (1909), reported that on prescribing thyroid tablets to cretins there

was a speeding up of eruption. Deciduous teeth persisting after the time to change to the permanent dentition should have been completed were shed in a short time and replaced by the corresponding permanent teeth. For example, a cretin, who at the age of $2\frac{1}{2}$ years had only two deciduous teeth, erupted twelve teeth during the one year of treatment. Another child who at $1\frac{1}{2}$ years had only two teeth, possessed the twenty deciduous teeth after two years of therapy. Another cretin over two years had only eight teeth which were supplemented to the full complement of 20 teeth while she received treatment for not quite a year. Another of the numerous cases cited ^{is} a patient who had no teeth at the age of one year two months ^{who} after one year of treatment had the full set of 20 teeth.

Differences in the dental effects of Hypothyroidism and Hypopituitarism.

Schour and Massler (1943) state that retardation of skeletal development is more severe in hypopituitarism. In hypopituitarism the retardation of tooth growth eruption follows more nearly that of the bony growth, with greater resultant harmony between dentition and bony base, but in hypothyroidism retardation of dental growth and eruption is less than bone growth and as a result the dentition is too large for the facial skeleton and jaws.

EXPERIMENTAL HYPOTHYROIDISM.

Dental changes.

Thyroidectomy presents certain difficulties because of the intimate relation both anatomically and physiologically, of the parathyroids to the thyroid. Schour and Massler (1943) indicate that in the rat, thyroidectomy usually involves removal of the parathyroid glands as well, and as Thoma and Goldman (1960) point out in the earlier experiments on the effects of thyroidectomy on the teeth, part of the result may have been due to hypoparathyroidism rather than hypothyroidism.

Biedl (1913) experimenting on thyroidectomised dogs, Erhlein (1914) experimenting on thyroidectomised rats, and Kranz (1914) experimenting on thyroidectomised pigs, and rabbits, found that the animals showed general retardation of growth, typical cretin-like skull, small teeth, and retardation^{of} eruption. Transverse furrows were found on the enamel due to structural defects. Todd and Wharton (1934) found delayed eruption and defective jaw growth in sheep that were thyroidectomised soon after birth.

Ziskin, Salmon and Applebaum (1940) from a study on rats operated on at birth, and at seven days of age, considered retardation of eruption time, dentine and root development, especially in the molar, as typical thyroprivic symptoms.

Ziskin and Applebaum (1914), showed that thyroidectomy in monkeys resulted in a retardation of up to 90% of normal in the rate of dentine opposition, as revealed by alizarinization. Calcification of the dentine was greatly disturbed, so that in most of the dentine formed after thyroidectomy, calcification was so slight that the Grenz Ray could not measure it. Enamel calcification was also disturbed. A definite line of hypoplasia of the enamel may be seen corresponding to the date of thyroidectomy. Muracciole's experiments (1957) on white rats confirm that there is a moderate hypocalcification of the dentine following thyroidectomy.

Glickman and Pruzansky (1947), used another method to produce the hypothyroidism. They used, propylthiouracil (a goitrogenic compound which was demonstrated by Larson et al in (1945) to inhibit the collection of radioactive iodine of the normal chick, by the thyroid made hyperplastic by the injection of thiouracil. Hawker (1950) summarises that these goitrogenic compounds act by virtue of their ability to interfere with the collection of inorganic iodine by the thyroid and its conversion into (thyroxine given to albino rats in their food. Because of the difficulties of thyroidectomy this method is probably better and the results more reliable. The drug was ground in with the diet, which was freely given, in two dosages of 0.1% and 0.03%. Of three groups of animals studied, only the one receiving 0.1% of the drug starting at 1-5 days after birth, via the transmammary route is reported here, on 65 rats. After 1-3 months the animals weighed less and were smaller than the controls. The jaws were smaller and there was retarded eruption of the incisors and molars. Microscopic examination revealed reduced endosteal and periosteal bone deposition. The appositional bone lines were more closely arranged giving the bone a compressed appearance. Somewhat similar effects were produced in one litter of young puppies after feeding with either thiouracil or organic selenium, in a report presented by English (1949). Selenium is a non-metallic element with a wide distribution in the soil of arid regions, is poisonous if consumed by animals if consumed in a concentration of more than ten parts per million for ten weeks, and is absorbed by plants in sufficient concentration to poison animals that eat them.

English (1949) in his interesting report also found the following results from his work on these treated dogs;

1. Hypoplasia of the enamel in a thiouracil treated dog.
2. structural defects of the dentine in a dog treated with large doses of selenium.
3. Structural changes in the supporting bone of the mandible in both thiouracil and selenium treated dogs.
4. Marked variation in size and shape of the mandibular condyles of all treated dogs, with histological indications of

of an untimely continuation of bone formation in the condyles of the selenium-treated dogs.

He showed that the gross lesions in these dogs were not unlike those found experimentally in thyroidectomy or in human cretins. He also drew attention to certain limitations in the experiment in that it was conducted on a single litter of four mongrel dogs, only.

The similarity to dental features seen in cretins has also been demonstrated by Hughs (1944) in rats.

Temporomandibular Joint.

Salmon (1936), Scow and Simpson (1945) both showed that thyroidectomy in the new-born rat results in severe slowing of general growth and differentiation. On the basis of radiographic examination, Scow and Simpson (1945) found that thyroidectomised rats differed greatly from the normal in that the rate of growth was reduced and that there was a delay in the appearance of secondary ossification centres. Histologic examinations of the tibia, metacarpal and caudal vertebrae confirmed and extended these observations; Scow, Becks, Simpson, Asling, and Evans (1950). Using this as a basis, Becks, Collins, Asling, Scow, Simpson and Evans (1948) studied the effect of thyroidectomy on the mandibular condyle, on rats thyroidectomised at birth. The results they found were that the cartilage of the condyle head remained wide for long periods as in young animals. However, the histologic characteristics of this condyle were not those of youth; the chondrocytes were not arranged in orderly columns. A distortion of the head of the condyle occurred, and consisted in widening and flattening, and the bone was denser than usual. Later at 105 days of age, the reduction in width of the cartilage the dense bony tissue resulted in a change back to what approached the normal controls. Recent studies by these authors have shown the importance of the mandibular condyle in the growth and development of the mandible, and the responsiveness of this structure to hormonal influences, Collins et al and Becks et al (1946).

Osteogenesis.

Burston and Shafer (1961) used a method for artificially expanding the premaxillary suture of the rat to investigate the effects of thyroid dysfunction on osteogenesis. They noted the effects of three groups;

1. Hyperthyroid, thyroxine treated rats, (see results under "Hyperthyroidism")
2. Hypothyroid, propylthiouracil treated rats, and
3. normal rats.

The data in all three series indicate that propylthiouracil evokes a more profound reaction at the site of mechanically-induced suture separation than that seen in either control or hyperthyroid animals. This reaction consisted of a greater thickness of osteoid along the inner suture faces, more prominent osteophytic formation, greater osteoblastic activity, and an increased cellularity of the connective tissue, between the two plates of bone. These results have to be compared with those of Ray et al (1950), and Marx, Simpson and Evans (1942) and since long bone growth, it is not surprising that the thyroid dysfunction effect on the growth of long bones is not the same as its effect on sutural growth.

Eruption of the Teeth.

Keith in (1911) was the first to advance that eruption depended on hormonal factors, and stated that both the thyroid and pituitary glands were responsible. Delayed eruption of the teeth was observed by Biedl (1913), Erdheim (1914), and Kranz (1914) in their experiments on thyroidectomised dogs, rats, and pigs and rabbits respectively.

Ziskin, Salmon and Applebaum (1940) from a study of rats operated on at birth and at seven days old, also found that retarded eruption was a feature of hypothyroidism. Eruption remained delayed when thyroidectomised rats were chronically injected with parathormone; treatment with thyroid extract on the other hand, effected partial restoration of tooth development, while the combination of both hormones produced complete recovery. Thyroidectomy performed on monkeys by Ziskin and Applebaum (1941), resulted in a decreased daily rate of dentine formation.

Hoskins (1927-1928) and Karnofsky (1939) both showed the reverse

effect on newborn rats who were put into a hyperthyroid state, and precocious tooth eruption occurred.

Baume, Becks, and Evans (1954) investigated the matter further, and observed the effects of thyroidectomy on the upper rat incisor. They state their results as follows;

1. Thyroidectomy reduced the eruption rate 45%, during a ten week period, while the size of the tooth structures remained 20-25% under normal average. Histologically, reduction of vascularity stunted growth as well as differentiation and early atrophy of the odontogenic epithelium were conspicuous thyroprivic symptoms.
2. Administration of growth hormone elicited a slight increase in eruption rate (10%) and in tooth size, while a considerable growth spurt of the maxillary bone over normal dimensions were observed. Histologically, connective tissues were rejuvenated, but young epithelial cells failed to undergo immediate histodifferentiation.
3. Injection of thyroxine increased the eruption rate (27%) more than dental dimensions. There was a marked increase in vascularisation in the dental structures and accelerated proliferation and histodifferentiation of epithelial tissues. Calcification, especially of the enamel matrix, however was deficient.
4. When both growth hormone and thyroxine were injected, simultaneously, the eruption rate and dental dimensions exceeded only slightly in the thyroxine treated group, but the histologic aspect revealed improved structure hardly to be distinguished from normal.

Becks (1957) states that following thyroidectomy in rats, the weekly rate of reduction of the bony fundus is lowered from a normal of 2.8mm to 1.5mm. The entire eruption process of upper incisors is nine weeks in the thyroidectomised rats whereas in the normal rat it is at the end of the fifth week. Thyroidectomy does not completely arrest the eruption rate; nevertheless, it does retard it considerably. Following thyroxine injections into thyroidectomised rats, the weekly eruption rate is raised to 2.38mm which is still below the normal of 2.8mm. Administration of growth hormone to thyroidectomised rats increases the weekly eruption rate to 1.8mm which is considerably below the normal.

When both growth hormone and thyroxine are administered

together the eruption rate is raised to 2.4mm. From the foregoing it can be seen that thyroxine restores the eruption rate to almost normal, while growth hormone has little effect on the eruption rate. Growth hormone seems to enhance alveolar growth.

Muracciole (1957) experimenting on white rats also found that thyroidectomy interfered with tooth eruption.

Shaw (1960) made a study to determine whether or not abnormal metabolic conditions effect the rate of tooth movement in rats. He induced hyperthyroidism and hypothyroidism into 60 rats, and a maxillary second molar was extracted from them and measurements made 33 days after. The results proved that both hyperthyroidism and hypothyroidism have no effect on tooth migration in rats.

The periodontium:

Degenerative changes in the gingivae have been reported in thyroidectomised animals by Ziskin and Stein (1942), Glickman and Pruzansky (1947) and Baume and Becks (1952) noted retardation of resorption of alveolar bone in thiouracil-induced hypothyroidism in animals.

Rosenburg, Goldman and Garber (1961) studied the effects of thyroid dysfunction on the periodontium of adult New Zealand rabbits. The thyrotoxic effects are referred to under the section "Experimental Hyperthyroidism". Myxedema was produced by administering subcutaneous injections of 1 millicurie of iodine 131 bimonthly over a period of 406 months. Gross findings in the myxedematous group were increase in weight, sluggishness, and the tongue was large broad and smooth. The skin was firm, elastic and dry, and the fur was coarse. Histologically, investigation revealed changes in the gingivae, which included hyperparakeratosis with some regions of keratosis; longer and more numerous rete pegs and intracellular oedema. The underlying connective tissue demonstrated interstitial oedema and areas of fragmenting fibres, with moderate disorganisation of the collagen bundles. The periodontal ligament showed a diminished cellularity, areas of hydropic degeneration, and fragmentation, and interstitial oedema. The bone presented a picture of relative inactivity, with reduced periosteal and endosteal bone deposition. The most striking feature was one of osteoporosis. The marrow spaces were found to be

large and more cellular.

Dental caries and Thyroid secretion.

As Gardner et al mentions in their interesting article on oral manifestation of endocrine disturbances in (1963)(August) perhaps the most controversial issue associated with hypothyroidism is whether or not there is an increase in dental caries, due to the disease per se.

The experiments of Muhler and Shafer (1954, 1955), Bixler, Muhler and Shafer (1956), Bixler and Muhler (1957), and Muhler and Shafer (1958, 1959, 1960) indicate a relationship between the secretory activity, of the thyroid gland and resistance to dental caries, by finding that the cariogenicity of a coarse-corn diet fed to albino rats was decreased by the addition of propylthiouracil. Their evidence seems convincing. The anticariogenic effect of dessicated thyroid is as effective as the administration of sodium flouride (1957). In their earlier studies (1954, 1956) they worked on weaning rats and showed that feeding them with dessicated thyroid reduced the incidence of caries, and that the administration of either iodine 131 or propylthiouracil increases the incidence of caries. In (1958) they experimented on mice, and in (1959) on adult rats. In this study, on adult rats, they found that the feeding of propylthiouracil resulted in a greater increase in the incidence of caries than occurred in weaning rats. The feeding of dessicated thyroid to adult rats did not reduce the incidence of caries. They also found that histologic changes in the thyroid and salivary glands of adult rats fed propylthiouracil resulted in extreme hyperplasia of the gland with increased cellularity and lack of colloid formation, and dessicated thyroid resulted in hypoplasia of thyroid glands with follicles lined by flattened cells and filled with colloid. These changes in the glands were similar to changes observed in weaning rats.

Shafer, Clark, Bixler and Muhler in (1958) studied the effect of thyroid function on salivary flow and viscosity in an attempt to provide some clue to specific alterations in function which might explain changes in the rate of dental caries. The effect of thyroid dysfunction on salivary flow and viscosity in the rat was

determined in a series of controlled experiments. Results indicated that feeding propylthiouracil, and radiothyroidectomy reduced the salivary flow and increased salivary viscosity. The results can be reversed and function restored by the administration of sodium thyroxine subcutaneously. The intramuscular injections of testosterone to thyroidectomised rats, partially restored the salivary flow. These data provide one explanation for the mechanism of alteration in the incidence of dental caries in the rat after disturbance in thyroid function, although the relation is probably more complex than indicated.

In their study of (1960), Shafer and Muhler report the following; Studies from our laboratories have constantly shown a relationship between dental caries, thyroid activity and the major salivary glands in rats. Hypothyroidism has invariably resulting in significant increase in caries incidence and alteration in salivary gland structure. Hyperthyroidism reduces caries as well as increased size and number of salivary granular tubules. To learn more about this mechanism and determine whether other antithyroid drugs act similarly, thiocyanate was administered at different levels to groups of rats and the effects studied. For comparison, two other recognised goitrogens, methimazole and dinitrophenol were also used as well as propylthiouracil and proteinase. These results showed that when potassium thiocyanate was stomach-tubed at a level of 5mg/rat/day, there was increase (10.2 lesions) in caries, but when stomach-tubed at level of 50mg/day, there was no change (8.2) in caries incidence when compared with controls (8.2). Dinitrophenol had no effect on caries (7.4), while methimazole increased (9.8) caries, and proteinase (7.1) decreased. Salivary studies also confirmed the caries response. Examination of the thyroids, in animals receiving these compounds confirmed their goitrogenic effects, although only thiouracil produces changes in the submaxillary gland granular tubules.

Haldi, Wynn and Law (1961, 1962), made further investigations as to the relation between thyroid function, salivary function and dental caries and report as follows; The experiments of Shafer and Muhler, indicate a relationship between the functional activity of the thyroid gland and susceptibility of resistance to caries.

In as much as their experiments were conducted on rats fed on a coarse corn particle diet with possible involvement of fracture of the tooth enamel, we have conducted somewhat similar experiments with a finely powdered high sucrose-diet. In one experiment albino rats were thyroidectomised and their control littermates subjected to a sham operation. The caries score of the thyroidectomised animals was 42 as over against 29 for their controls. In a second experiment triplicate littermates were fed, respectively, the control diet, and the same diet containing either 0.05% thiouracil or 0.1% dessicated thyroid. The caries score on the three diets were respectively, 17, 25, and 10. It would appear from these two experiments that the loss or reduction of the thyroid secretion to the body economy resulted in an increase in caries, whereas an increase in the thyroid hormone resulted in a decrease in caries. In a third experiment triplicate littermates were sialoadenectomised and fed the same diets as in the second experiment; resulting in caries scores respectively of 46, 44, 41. A fourth experiment was conducted on twenty groups of animals to compare the effects of ingestion of dessicated thyroid in the food and by the stomach tube. The administration of the thyroid by either route reduced the caries rate. In a fifth experiment 20 groups of animals were given the control diet plus water to drink, control diet plus 20ppm potassium iodine in the diet, and control diet plus 20ppm potassium iodine in the drinking water. The caries experiments support the idea expressed by other investigators that the thyroid-dental caries relationship is mediated by the salivary glands. Elucidation of the mechanisms involved must await further experimentation.

These results of Haldi et al (1961, 1962) support Shafer and Muhler's work, and ruled out the suggestion that the hard corn diet may have been responsible for the rise in caries incidence. Their results differed in only one respect from the latter's in that the cariogenic effect of propylthiouracil was still evident, though to a lesser extent, in animals that were sialoadenectomised than in normal ones, whereas the latter reported a full loss.

Nielson et al (1961), who showed that the rate of oxygen consumption by excised heart, muscle, kidney, liver and brain, of

thyroidectomised rats followed a similar pattern to that of the whole animal, interpreted the results of Fawcett and Kirkwood's work (1954) to indicate that the parotid and submaxillary glands function to control the level of thyroxine in the blood stream by de-iodinating the hormone and recycling the iodide ion to the thyroid via the saliva, gastrointestinal tract, and blood stream. Carrying this idea a step further, Ryan and Kirkwood (1955) suggested that the increase in caries as a result of feeding dessicated thyroid which had been reported by Shafer and Muhler (1954-1960) might be explained as due to an increased concentration of the iodide ion in the saliva, assuming that the iodide ion makes the teeth more resistant to caries. This is the reason why Haldi et al (1961,1962) conducted their fifth experiment mentioned earlier. They state that whilst recognising the studies of Ruegamer (1955) indicating that the salivary glands did not have the de-iodinating function postulated by Fawcett and Kirkwood (1954), and regardless of the mechanism involved, iodide clearance by the salivary glands appears to be correlated with thyroid activity as mentioned by Frienkel and Ingbar (1953,1955). The fifth experience of Haldi et al (1961-1962), would appear to rule out the explanation offered by Ryan and Kirkwood (1955) for the thyroid - salivary glands - dental caries relationship and likewise the possibility that the increased caries susceptibility in sialoadenectomised animals might be attributed to the resultant loss of iodide, normally provided by the saliva.

Gardner et al (1963) summarising the results of Shafer and Muhler (1954-1960), and others, state that the higher caries incidence is probably due to accumulation of carbohydrates because of decreased washing action of the saliva and the decrease of its iodide ion content. It would appear however, that the results of Haldi et al (1961,1962) negates the reference to the place iodide ion has.

It would seem therefore that at this stage the main factor is the effect of the thyroid function on salivary flow and viscosity. It is well established that a diminution in the rate of salivary flow has a marked effect on caries incidence in experimental animals. However, further clarification of this thyroid-salivary glands-dental caries relationship is needed.

THYROIDITIS.

The term "thyroiditis" denotes inflammatory changes within the gland, of unknown aetiology, of which the usual types are Hashimoto's (by far the most common), Granulomatous or subacute, and Riedel's thyroiditis. Lisser and Escamilla (1962).

HASHIMOTO'S THYROIDITIS, Lymphadenoid goitre.

This disease occurs most frequently in females and is characterised mainly by local pressure effects (hoarseness and dysphagia), nervousness and fatigue. It frequently occurs after I^{131} treatment. There is a relatively slow enlargement of the thyroid which differentiates it from symmetrical malignancy of the gland. Treatment is by subtotal thyroidectomy best; but steroid therapy or irradiation may be all right, Prognosis is good. Selye (1949), Lisser and Escamilla (1962).

Oral manifestations are the effects of local pressure as mentioned above.

GRANULOMATOUS THYROIDITIS, subacute thyroiditis:

This condition which is characterised by the appearance of giant cells, is very much more common in females, and occasionally in children. Chief symptoms are lassitude, fever, tachycardia, sweating, pharyngitis, in its onset, followed by a slightly enlarged gland, which is tender and painful aggravated by deglutition, and the pain may be radiated to the ear and mandible. Aetiology is unknown, but the mumps virus has been suspected, Eylan et al (1957), and pharyngitis and other disorders, Volpe and Johnson (1957), Vanderlinde and Milne (1960).

Oral manifestations: Pain in the lower jaw is one of the cardinal symptoms, Lisser and Escamilla (1962), Tolman and Gibilisco (1962). The latter mentions that the patient may first consult a dentist because of pain in the area of the angle of the mandible. They studied 40 cases seen in the Mayo clinic in two years, nine of which were men, the median age being 42, 73% under 50 years of age. Pain in the neck was the most common symptom, and periauricular pain occurred in 40%, and mandibular pain in 37%. Two of these

THE PARATHYROID GLANDS.

INTRODUCTORY.

The parathyroid glands consist of two small pairs of ovoid, yellow-brown coloured, granular tissue closely applied to the back of the thyroid gland, and within its fibrous capsule. Each gland is about 6x3.5x1.5mm in size, their total weight being about 1gm. The glands vary considerably in size, weight and number, Cunningham (1947), Gilmore (1938) states that 6% of persons have three parathyroids, and 6% have five.

The glands develop from the dorsal diverticulum of the third and fourth pharyngeal pouches, Cunningham (1947). They have a common origin with the thymus, Hawker (1950).

Histologically the gland structure consists of interconnected trabeculae of epithelial cells with strands of fibre-alveolar tissue containing a rich supply of capillaries surrounding them, Cunningham (1947). The cells are mainly the "principle cells" or "chief cells" which are closely packed together arranged in acini around a lumen containing colloid, and the less numerous oxyphilic cells, which are larger. Another type of cell, the "Wasserhelle" cell has been described, Keating (1947), but is probably a "chief cell" with a vacuolated appearance, Albright and Reifenshtein (1948). Ham (1953) and others, consider that the parathyroid hormone (or parathormone) is produced only by the chief cells, and that the function of the oxyphilic cells is unknown. The Parathyroid gland assumes its adult size at puberty, and with increasing age, the gland shows histologic signs of decreased activity.

Historically there was knowledge of the condition of tetany 150 years ago, but its association with the parathyroids was not known. Sandstrom (1880) a Norwegian physician first discovered the parathyroids, and about the same time so did Barber of England. Sandstrom gave the glands the name parathyroids but believed them to be merely vestiges of embryonic tissue. Kohn (1895-9) first recognised that they were independent organs and gave them the name, "epithelial bodies". Since then, the parathyroids have been proven to be important endocrine organs, and in spite of their very small size, their removal is a fatal operation unless

patients consulted a dentist first because of the jaw pain. They state that diagnosis is difficult and often passes unnoticed, and that the dentist should familiarise himself with the condition.

Treatment: irradiation, propylthiouracil, cortisone, penicillin, and occasionally subtotal thyroidectomy have been suggested in that order, Lissner and Escamilla (1962). The prognosis is usually good and the pain symptoms subside on correct treatment, Tolman and Gibilisco (1962).

RIEDEL'S THYROIDITIS, (Struma).

This condition is extremely rare, occurring more in females. It is usually superimposed on nodular goitre, and produces pressure symptoms of a greater degree than in the other thyroiditis diseases, which effects the pharyngeal area, producing the oral manifestations.

Treatment is subtotal thyroidectomy, and prognosis is usually good, except for the consequent hypothyroidism, Lissner and Escamilla (1962).

substitution therapy is maintained. Their chief function is the regulation of calcium and phosphorus metabolism.

Parathyroid Hormone (Parathormone).

An active extract was first isolated by Collip (1924) and Hanson (1925) from animals and investigated by him and others (1934)

Mendl of Vienna (1926) made further observations and proved the connection of the parathyroids to osteitis fibrosa cystica. Aub et al (1929) initiated a series of studies in mineral metabolism which established the link between the glands and skeletal changes.

Patt and Luckhardt (1942) observed that the chief, if not only stimulus to parathyroid secretion is a lowered calcium ion concentration in the blood plasma.

Parathyroid hormone is destroyed by protein digestion and is therefore ineffective if administered by mouth, Keating (1947).

McLean and Budy (1961) report that during the year (1960), some 35 years after the first preparation of an active extract of the parathyroid glands, the chemistry and physiology of the parathyroid glands entered a new era. For the first time the hormone was isolated in a pure form, and analysed, and small amounts were made for experimental purposes, supplementing the crude extracts, upon which virtually all the work on the parathyroid gland hormone physiology was based. Work with this new pure hormone has already clarified some important problems, and it may be confidently expected that other major advances will follow. Rasmussen and Craig (1961) isolated the pure hormone by sequential phenol extraction, and found it to be a protein exhibiting a certain degree of instability. All purified preparations of the hormone have shown both calcium mobilising and phosphaturic activity, in comparable amounts. It is now known that the parathyroids secrete only one hormone.

Physiology, of the parathyroid hormone is therefore becoming more and more clarified. Several theories have been presented as to its mode of action, but it is not known definitely yet how it

affects calcium and phosphorus metabolism. It is generally agreed that its chief function, if not, its only one, is to preserve the normal concentration of calcium ions in the body fluids, Keating (1947), the difference of opinion lies in the mechanisms by which this is accomplished.

It is well known that the removal of the parathyroids causes;

1. Decrease in phosphorus excretion in urine.
2. Increase in level of serum phosphorus.
3. Decrease in serum calcium level,
4. Decrease in urinary excretion of calcium.

Administration of parathyroid extract gives the reverse reaction.

There has been a great deal of research on the action of the parathyroids, through experimental parathyroidectomy, administration of parathyroid extracts, and through observation in man with diseased parathyroid glands.

One theory for the action of parathormone is that it acts directly on the bones, causing their demineralisation and that the electrolyte changes are secondary as suggested by Thompson and Collip (1932) and confirmed by Jaffe (1933) and Selye (1942). The calcium-X theory of Greenwald and Gross (1925) is similar.

Another theory is that suggested by Cohn, Cohn, and Aub (1942) and Albright and Reifenshtein (1948) which states that the hormone affects in some way the phosphorus in the body fluids so as to render it more readily excretable by the kidneys producing a decrease in serum phosphorus which in turn upsets the calcium - phosphorus equilibrium in the body causing a secondary increase in serum calcium by withdrawing calcium phosphate compounds from bones. However, Selye (1949) gives tangible reasons eliminating the kidneys as the primary site of parathormone action. On the other hand, Albright and Reifenshtein's theory has a good deal of support, including that of Thoma and Goldman (1960).

Albright and Reifenshtein (1948) remark that just as they have had to admit that there may be a direct action of the hormone on the bone tissue (vide supra), the chief proponent of the opposing school, Collip (Neufeld and Collip, 1942) has swung somewhat to their point of view. However, they still feel that the main

action of the hormone is on phosphorus and calcium metabolism.

Weinmann (1945) has a theory which states that the hormone acts on the bone to withdraw calcium by dissolution, through the medium of the osteoclasts, mobilising mineral from them.

Ham (1953) comments that the most logical theory so far is that the hormone acts primarily on the calcium, then on phosphorus, the site of action being the blood rather than bone, the bone effects being secondary..... However Tweedy et al (1947) proved that after bilateral nephrectomy parathormone injections had no influence on distribution, retention and excretion of radiophosphorus. This shows that the hormone has no action on blood calcium and phosphorus, unless the kidneys were present.

Selye (1949) states that the theory which appears to be most readily compatible with all the pertinent observations, assumes that parathormone acts primarily upon the osteoblasts, by transforming them into osteoclasts, which cause bone absorption with consequent discharge of skeletal minerals into the blood stream. But he adds that even this theory has its limitations, and that the possibility must not be excluded that the hormone acts directly both on the kidney and the skeleton.

Black (1953) carried this idea forward and remarked that in all probability the hormone exerts its influence on both sites, perhaps the phosphate diuretic action of the kidney being more important than the direct decalcification of bone, since even moderately severe hyperparathyroidism may exist without demonstrable evidence of skeletal changes.

McLean and Budy (1961) state that it is conceded now that bone is one of the primary targets of the biologic activity of the hormone, and there is also agreement that it exerts its influence upon cellular constituents, and does not affect the solubility of bone mineral in body fluids.

Neuman and Neuman (1958) declared that the mineral of bone exists in two forms ; 1) labile, reactible and exchangeable ~1%.
2) stable, nonreactible or non-exchangeable ~99%.

Vincent and Hammont (1960) called these two fractions "metabolic bone"

and "structural bone". Woods and Armstrong (1956) and Talmage et al (1960) have demonstrated that the hormone has access to the stable calcium bone to the fluids of the body. There is general agreement that the parathyroids, by virtue of their action to regulate osteoclastic bone resorption, including its stable fraction, are responsible for maintaining the calcium ion concentration of the plasma, and for correcting deviations from the normal. There are however, divergent views concerning the transfer mechanism of labile calcium from the bone to the blood. Recently, Neuman et al (1961) have advanced the view that this is under the control of the parathyroids also.

Rasmussen (1961) pointed out that osteoclastic bone resorption, whilst under the control of parathyroid activity, is not exclusively so. This was pointed out by Jowsey et al (1958) who found that resorption was not entirely halted in thyroparathyroidectomised dogs.

McLean and Budy, (1961) also state that contrary to earlier views it is now proposed that the hormone influences the absorption of calcium from the gastrointestinal tract, being synergistic with vitamin D in this respect. Talmage and Elliott (1958) proved this on parathyroidectomised rats, whose rate of absorption of radiocalcium dropped some 50% within 2-4 hours.

Calcium and phosphorus metabolism:

In addition to the above remarks as to parathyroid hormone physiology, the following will be of interest.

Calcium is of major importance to the body, and in health 9-11mg is present in every 100ml of blood. This has been divided into diffusible calcium of which portion is in the ionizable form, and the non-diffusible un-ionized form. The daily calcium requirements for man is approximately 0.8gm/day. Milk is the best source, but leafy vegetables, eggs and cheese are also good sources. The principle inorganic anions associated with calcium in the organism are phosphate and carbonate. The calcium of the blood is particularly associated with inorganic phosphate, the proteins, and hydrogen ions. Any change in these affects the state of the calcium, so there is an equilibrium between calcium and phosphorus, and between calcium in the blood and that excreted. More than

98% of the calcium in the body is present as a calcium phosphate-carbonate compound in the organic matrix of bone and teeth, small amounts being in the body fluids. Normally calcium deposition and absorption from bone are going on all the time. If calcium metabolism is affected when the tooth is being formed an absence of calcification may occur, however if the tooth is already formed no decalcification takes place. There is no interchange of calcium in human teeth in adults. Tooth decay during pregnancy certainly does not arise from mobilisation of calcium from the teeth to the blood stream to the placenta and child. Therefore the ever present axiom, "A tooth for every child" which originated in Greek times is utterly false. Gardner et al (1963).

A number of factors are concerned with the process of bone formation;

1. The calcium and phosphorus blood levels, and form they exist in.
2. the pH of the blood.
3. the presence of parathormone.
4. calcium and phosphorus intake in food.
5. Acidity or alkalinity of the food, and intestinal contents.
6. The presence of Vitamin D.
7. local conditions in the calcifying cartilage,
8. phosphatase enzymes.

The function of calcium is as follows:

1. bone and tooth formation,
2. it is essential for the conversion of prothrombin to thrombin,
3. it opposes the action of sodium and potassium ions and decreases muscle and nerve irritability,
4. it diminishes the permeability of cell membranes,
5. it is essential for the rhythmic contraction of the heart,
6. it may decrease allergic reactions,
7. it exerts a significant effect on the distribution of other minerals. Gardner et al (1963).

The function of phosphorus are:

1. it is present in all tissue cells in organic combination,

2. it plays a considerable role in muscle metabolism,
3. phosphorylated fats are important intermediaries in fat transport and metabolism,
4. the phosphate of calcium is the chief component of bone (inorganic)
5. regulation of pH in blood and urine.

Organic phosphorus is in equilibrium with the organic phosphorus. Hawker (1950)

The calcium:phosphorus ratio is 2:1 in bones and teeth. The phosphorus appears only in small amounts in body fluids.

The phosphatase enzymes are also important, and are considered to be a product of osteoblasts, the proliferating cartilage cells, and the periosteal cells. Its presence in the intestinal mucosa aids in the digestion of phosphorus compounds. Large amounts of phosphatase have been found in areas of active calcification, especially young growing bones. These enzymes may be either acid phosphatase or alkaline phosphatase.

Bone Ossification. is either of the intramembraneous type (mandible, and flat bones of the cranium) or intracartilaginous type (base of skull, bones and limbs and trunk), and develops from centres of ossification, within the organic matrix of cartilage (or membrane) and spreads to the whole area. It seems that the immediate cause of calcification may be a localised increase of phosphate ions, resulting from a splitting off of inorganic phosphate from organic phosphate compounds by alkaline phosphatase, which is produced by the osteoblasts. Bone resorption is mediated by osteoclasts, and occurs regularly both in normal and pathologic conditions. They dissolve organic and inorganic material of the interstitial substance of bone simultaneously.

It is clear that there is a relationship between the parathyroids and the anterior pituitary as observed in pathologic conditions, but it has not been established that there is a parathyroidotrophic hormone. There is also apparently a parathyroid-adrenal relationship and also one with the thyroid and the pancreas, Albright and Reifstein (1948), Cushing and Davidoff (1927).

HYPERPARATHYROIDISM, (Von Recklinghausen's Disease, Generalised Osteitis fibrosa, osteitis fibrosa cystica)

Rosenberg and Guralnick (1962) state that hyperparathyroidism has evolved from a rare to a not uncommon disease, during the past 30 years. This is not due to an increase in incidence but rather to better recognition of the many clinical forms of the disease and improved diagnostic methods, Albright et al (1934), Albright (1948), Cope (1960).

Von Recklinghausen first described the disease in (1891). Up till then it had been confused with osteomalacia and osteitis deformans. Hart (1904) spoke of it as "osteomalacia with multiple giant cell sarcoma and cysts". Others have used the term "giant cell tumours", but Thoma and Goldman (1960) remark that osteoclastomas and cysts are not a constant feature. The first parathyroid adenoma was described by Santi (1900) who did not suspect that such tumours could cause extensive bone destruction. Askanazy (1904) reported a case of thyroid tumour, which he thought was possibly a parathyroid tumour. Subsequently, the parathyroid theory of osteitis fibrosa was clearly formulated by Schlagenhauser (1915) and he even suggested that parathyroidectomy may be the logical treatment. Mandl (1925) attempted this method of treatment in Vienna with excellent results. Hoffheinz (1925) demonstrated that hyperparathyroidism was definitely associated with bone disease. Following Collip's discovery of the parathyroid extract (1925) much experimental research occurred clarifying the matter further, Greenwald and Gross (1925), Hueper (1927) etc. The final proof of the parathyroid aetiology was given by Jaffe, Bodansky and Blair (1930), who reproduced the characteristic bone lesions in animals by overdose of parathyroid extract. Johnson and Wilder (1931) showed that the disease was not related to osteomalacia as vitamin D did not affect it.

The term "hyperparathyroidism" was introduced by Barr, Bulger, and Dixon (1929), and Barr and Bulger (1930) reported on several cases of tumours and hyperplasias. Hunter (1931) presented an important and clarifying lecture in London on the disease.