Albright, Aub and Bauer (1934) reported on several cases and found that renal stones was a frequent occurrence in the disease in association with skeletal changes, and showed that hyperparathyroidism can occur without many of the extreme changes seen in the originally described condition of von Recklinghausen. In some cases, skeletal involvement was entirely lacking. Albright et al (1934) made further investigations in following years and examined some 68 cases, and they reported their findings, Albright (1948), Albright and Reifenstein (1948). They arrived at the conclusion that hyperparathyroidism was much more prevalent than formerly supposed. It was originally considered as rare, but now it is felt that some 3-5% of all cases of kidney stones have a hyperparathyroid origon. Selye (1949). Lisser and Escamilla (1962) state that in the University of California Medical Centre, 90 cases were recognised and verified in slightly over five years, with only two negative operations. They also state that bone involvement occurrs in 11% of cases, Cope (1944) showed that of 78 cases, of the disease seen in Massachusetts General Hospital which included the 68 cases examined by Albright et al (1934), that 43 had renal stones without any bone changes and only 23 showed the classical changes in the bohe. These findings were confirmed by Keating and Cook (1945) at the Mayo Clinic in an analysis of 24 cases. It is this that led Albright (1948) to conclude that the primary site of action of parathyroid hormone was on the kidneys.

<u>Aetiology:</u>

Selye (1949) gives an aetiological classification of hyperparathyroidism as follows.;

1. <u>Primary hyperparathyroidism</u>, due to (a) Parathyroid adenoma,
(b) Diffuse parathyroid hyperplasia.
(c) excessive parathyroid hormone therapy.

2. <u>Secondary hyperparathyroidism;</u> (resulting from increased requirement for parathyroid hormone) caused by;

a) Renal insufficiency (Renal Rickets, Renal fibrocystic osteitis, renal osteitis fibrosa) This chronic renal failure causes bone changes similar to those seen in rickets but actually due to osteitis fibrosa. Excess parathyroid hormone

apparently is secreted as a compensation to the hyperphosphatcemia and acidosis caused by the kidney deficiency.

b) Rickets and destructive bone disease,

which calls for increased parathormone because of bone destruction and the derangement of the calcium and phosphorus metabolism.

Rosenberg and Guralnick (1962) studied 220 patients with hyperparathyroidism at Massachusetts General Hospital of which 140 were females, and 79 males, and the age range being from 12-74 (highest incidence being in the fifth and sixth decade) 189 had adenoma, 26 had hyperplasia of all four glands, and eight had carcinoma. Lisser and Escamilla (1962) report that the usual cause of hyperparathyroidism is one or more parathyroid adenomas of 104 cases, examined 91 were adenomatous, (84 single adenoma, seven multiple adenomas) ten were hyperplastic, and three carcinomatous. In about 15% of cases, the tumourous, were aberrant (eg. mediastinal). Occurrence is approximately equal in the sexes and most frequent in the 40-50 age group. Up to 1960, 23 cases had been reported in children, and in some of these cases, the disease was inherited. Duodenal ulcers and pancreatitis are complications of the disease in some cases. Thoma and Goldman (1960) and Chaudhry et al (1958) state that the disease is three times more common in women than men, which is different to the statement of Lisser and Escamilla (1962) and Selye (1949), who states that itis equal in both sexes. This was confirmed by Silverman et al (1962) who revieved 42 consecutive dentulous patients with hyperparathyroidism and found that there was no correlation between sex and age and any aspect of the disease.

Albright and Reifenstein (1948) gives the following causes for parathyroid enlargement by hyperplasia;

1. Rickets or osteomalacia,
2. Pregnancy.
3. Renal insufficiency of the type associated with phosphate retention.
4. Calcium deprivation.

All four conditions tend to lower calcium levels, and he concluded that adenoma formation may be due to the following sequence -

1. Some condition causing a lowering of serum calcium level,
2. stimulation of all parathyroid tissue.
3. formation of many circumscribed "germination centres"
4. loss of the part of one or more of these centres of their property of being controlled by normal stimuli (adenoma).

Rogers and Keating (1947) remark that parathyroid pathology cannot be explained by hypertrophy alone, which leaves room for much more investigation.

Clinical Findings of Primary Hyperthyroidism.

The onset of the disease is rarely acute, usually insidious with slow progression.

Lisser and Escamilla (1962) list the symptoms and signs of the disease under three heads; (this is similar to the classification of Albright and Reifenstein (1948)

Those due to hypercalcaemia;

1. Constipation, and abdominal pain,
2. Weakness and lethargy.
3. Psychic disturbances, delusions, memory impairment.
4. Loss of weight.
5. Anorexia, nausea, severe dehydration, leading to prostration.
6. Symptoms of metastatic calcification in any part of the body, particularly the lungs, gastric mucosa, and kidneys. (only in advanced cases).
7. Hypercalcaemic keratropathy (calcium deposits in cornea).

Those due to urinary tract disease;

1. Polydipsia and polyuria, (calcium diabetes insipidus)
2. Ureteral colic from kidney stones; occasionally milky urine or gravel.
3. Fever and pain from complicating urinary tract infection,
4. Hypertension probably related to renal damage.

Those related to bone disease (11% of cases);

1. Spontaneous pathological fracture of bone cysts,
2. vague aches which may lead to incorrect diagnosis of arthritis,

a common initial symptom of the disease.

3. bending of the long bones, due to generalised decalcification with resultant shortening of stature, pigeon-breast deformity, occasional bone swelling.

4. sore, swollen gums due to bone tumours or cysts (a form of epulis)

5. loss of teeth, due to disease of mandible and maxilla (a late symptom).

Shafer, Hine and Levy (1963) state that pathologic fracture may be the first symptom of the disease, although bone pain and joint stifness are frequently early symptoms. In Silverman's (1962) 42 cases, the most common early clinical finding was urinary tract stones, which was present in 33 of the patients.

Rosenberg and Guralnick (1962) in a study of 220 patients, found, that the chief symptoms were as follows; bone disturbances 55 patients, epulis (ginat cell tumour) ten, gastrointestinal disturbanc 17, fatigue and others 38, genitourinary tract 122. Of the 220 patients, 119 had some form of bone disease, 178 had some form of renal disease, 33 had some form of gastrointestinal disturbances. In 47 patients the lamina dura was absent on dental radiographs.

Thoma and Goldman (1960) remark that the outstanding feature of the disease is decalcification of the skeleton, producing osteoporosis (generalised osteitis fibrosa), and in some cases, tumours and cysts (osteitis fibrosa cystica), and renal complications.

<u>Incidence of oral involvement</u> Thoma and Goldman (1960) remark that several patients who came under their observation had oral jaw lesions first, such as giant cell tumours and cysts of the jaws, which turned out to be osteoclastomas.

Black and Ackerman (1950) also pointed out that there is a high incidence of involvement of the maxilla and mandible, and in seven of 22 cases, swelling of the jaw was the predominent symptom.

The frequent finding of osteoclastomas and cysts may be due to trauma occuring during the course of the disease, Beneke(1904). Pommer and Hamptom (1919), showed that intermedullary haemorrhage resulting from trauma caused resorption of bone and cyst formation. The presence of Osteoclastomas also may be due to extravasation of

blood and accumulation of pigment. Hunter (1931) however believed that they were due to exaggerated osteoclastic activity, causing the aggregation of a large number of foreign-body giant-cells as a response to excessive secretion of parathormone.

Cohen and Kelly (1933) have reported a female patient aged 48 years, with a history of the disease having started nine years previously in the right side of the mandible. Murphy et al (1950) reports 25 cases with four having jaw involvement.

Weinmann (1945) presented three cases of hyperparathyroidism following glomerula-nephritis, with typical jaw changes. Cahn (1951) commented that occasionally cases of renal osteodystrophy occur in which there is no parathyroid hyperplasia.

Browne (1958) reports a case first diagnosed in the jaws by a dentist. The patient, aged 22, had some teeth removed following a swelling of the jaws. The swelling did not disappear, but increased in size and the patient was referred to the Glasgow Dental Hospital. The only other symptoms were occasional headaches and a feeling of lassitude. Radiographic and blood chemistry tests were made which revealed the presence of hyperparathyroidism.

However, it must be accepted that only occasionally are these changes in the jaws, the first signs of the disease.

Laboratory findings; According to Lisser and Escamilla (1962) they are;

1. Serum calcium; Is elevated and its consistant elevation is the most important diagnostic finding. If the disease is suspected clinically and the serum calcium test negative, repetition in another laboratory is recommended. Higher levels may be also evoked by restricting dietary phosphate. The level reached is usually 11-18gms%, but levels of 29.4mg% have been reported. (normal range is 9-11mg%). Hypercalcaemia of hyperparathyroidism is characterised by normal distribution, between protein bound and unbound fractions. High levels are not lowered by cortisone. Logan (1939) experimented and found that the blood calcium level rose within the first hour after a large injection of parathormone which indicated that it s affect on bone would be almost immediate.

2. Serum Phosphorus; It is characteristically lowered to 1.5 to

2.5mg% (normal is 3.4mg%) and is almost diagnostic together with the hypercalcaemia, but normal values are found in about 60% of cases. It may be elevated if glomerular filteration rate is decreased. Logan (1939) demonstrated experimentally that the serum inorganic phosphorus level usually decreased during the first hour after a large injection of parathormone, and phosphate excretion increased, which confirms what was stated above as to the rapidity of the hormone's action.

3. Serum alkaline phosphatase; Level is elevated if bone is involved with roentgen osteitis; ie 20 or more Bodansky or S.T and R. units. (Normal is five or less units), Albright et al (1934) points out that the bone involvement was necessary for this to be apparant, and is an index of the degree of resorption. Coleman (1954) stated that this test should only be used to determine the degree of bone disease once the diagnosis has been established.

4. Tubular reabsorption of phosphorus; Is low, under 76% whereas normal is 80-90%. It may be elevated to low normal level by strict phosphate deprivation, but phosphate loading will demonstrate a low TRP.

5. Hypercalcuria; Urine Sulkowitch Test; Is strongly positive, indicated by prompt appearance of dense cloud, and is classified as 3+ to 4+ indicating hypercalciuria. A simple screening test which should be done first, as if it is negative, hyperparathyroidism is unlikely unless uraemia is present. Cahn (1952) describes this test (see below).

6. Hyperphosphaturia; is usually present.

7. Urinalysis may give evidence of renal gravel or lithiasis; secondary, infection may result in albinuria, white blood cells and casts; specific gravity is usually low; Bence Jones-protein is occasionally present in advanced skeletal disease.

Albright and Reifenstein (1948), comment that if the patient has a marked degree of the disease, the normal levels of calcium and phosphorus in the blood will be sufficiently altered, to be conclusive in diagnosing the disease.

Selye (1949) adds that in mild, chronic cases, the calcium content of the blood may occasionally remain normal, perhaps because of such compensatory reactions as are known to occur under

the influence of prolonged exogenous parathyroid hormone administration. He also remarks that in the final stages of severe hyperparathyroidism, if urinary excretion of phosphates is severely impeded by renal insufficiency there may be no drop in blood phosphate.

Keating (1947) however stated that, regardless of its manifestations, primary hyperparathyroidism is always characterised by an increase of calcium and reduction of phosphorus in serum. But this does not appear to be so as Snapper (1949), considering the matter further, pointed out that in some cases, the blood chemistry may be within normal limits, since the kidney tubules normally absorb sufficient calcium to maintain the normal blood levels. In such cases, the calcium is excreted, which makes urine tests of great importance. He reported that several patients with recurrent jaw tumours had a normal blood chemistry, and it was the calcium excretion studies that showed a negative calcium balance. He also reported a case of recurrent osteofibroma of the mandible and maxilla, with the only laboratory findings being a negative calcium balance, and in which exploration of the neck disclosed a parathyroid adenoma.

Levy (1952) reported a similar case. Multiple lesions were found in the maxilla and mandible, which on pathologic examinations appeared to be due to a giant-cell tumour. Although there were no typical laboratory findings, explanation of the neck, disclosed a Parathyroid Tumour.

Schneider (1953), and others have stressed the wide variation that occurs in these levels in the disease between patients, stating that serum calcium may go as high as 24mg.% while phosphorus is decreased as low as 1mg.%

Urinary analysis is a very important diagnostic measure in hyperparathyroidism. In normal conditions about 75% of the ingested calcium is excreted in the faeces and about 25% by way of the urine. Cahn (1952) indicated that the opposite is true in hyperparathyroidism. Thoma and Goldman (1960) remark that in primary hyperparathyroidism, there is increased urinary secretion of both phosphorus and calcium. The calcium precipitates out as a phosphate salt,

especially if the urine is alkaline, since the phosphate ion is always in excess. If the urine is acid and oxalate is present, calcium oxalate will form, and precipitation may occur in the kidneys or other parts of the urinary tract, with resultant gradual impairment of renal function.

When there are signs and symptoms of hyperparathyroidism, with apparent normal blood chemistry, carefully controlled studies of calcium excretion in the urine must be done and these are best done under strict medical control in hospital, Southam (1959). The Bauer-Aub diet is the one generally used (100 125mg calcium day) and the patient is kept to this for three days and then a 24 hour specimen of urine is examined for calcium. Normally a patient on this diet would not excrete more than 100-150mg calcium per day. Any amount above this would be significent of a negative calcium balance. Thoma and Goldman (1960) indicate that in hyperparathyroidism three times the normal amount is usually excreted.

The Sulkowitch test is a simple screening test which is easily done in the laboratory and ought to be done first. It is referred to by Cahn (1952), and is as follows: the patient is instructed not to eat any milk or cheese for three days; the morning specimen of urine of the fourth day, is examined, and it should be neutral or slightly acid with litmus. If it is alkaline a drop or two of glacial acetic acid is added till slightly acid. Five mls. of the urine are placed into a test tube and about 2mls. of "Sulkowitch solution " (Oxalic acid 2.5gm., Ammonium oxylate 2.5gm., glacial acetic acid 150.0ml., distilled water q.s. add 150 0ml.) are added. The speed in which the precipitate forms and its degree of intensity is noted, and the results are registered as from zero to 4. A zero test would indicate a hypocalcaemia, while a 3-4 would indicate a hypercalcinuria and strongly suggest a hypercalcaemia. It is only a rough, but nevertheless quite accurate test, and if there is a constantly high positive Sulkowitch over a period of time, more detailed studies of urinary calcium excretion should be done.

Radiographic Findings:

As Shafer, Hine and Levy (1963) point out, the radiographic findings in this disease are of particular importance. The bones

of persons with bone involvement shows a general translucency as compared with normal people. Later, sharply defined round or lobulated radiolucent areas develop. If this occurs in the mandible, it must be carefully differentiated from an ameloblastoma which frequently has the same appearance.

The first evidence of decalcification appears as a general, fine, milary or granular mottling which is evidence of osteoporosis. Albright and Reifenstein (1948), Thoma and Goldman (1960) makes special referrence to the even ground-glass appearance of the cranium and state that in their experience, it is not met with in any other condition, except renal osteitis fibrosa generalisata or renal rickets. The thickness of the skull is not affected.

A flat film of the abdomen may show multiple renal or urethral calculi as well as nephrocalcinosis, which usually occurs in cases of severe and long standing hyperparathyroidism, Rosenberg and Guralnick (1962).

The round radiolucent areas in the bone referred to above, have been regarded as osteoclastomas, or bone cysts, or as Albright and Reifenstein (1948) describe as "pseudo-cysts". Keating (1947) states that a sub-cortial cyst is most suggestive of hyperparathyroidism. Sometimes the cysts will appear multilocular due to irregular erosion of the cortex, Cahn (1948), and in rare instances they will expand the surface. Coleman (1954) Thoma and Goldman (1960), The bones most affected in generalised osteitis fibrosa, in order of incidence are; the long bones, calvarium, mandible maxilla, pelvis and phalanges. The Maxillary sinus may become invaded by giant-cell tumours of the maxilla. The mandible and maxilla may both be the seat of large osteoclastomas and the mandible, may show evidence of osteolysis, Thoma and Goldman (1960)

Radiographic Dental Findings;

Dental films are of special value, due to the sharp contrasts possible between the decalcified bone and the teeth. The spongiosa assumes either a granular mottled appearance, or enlarged marrow spaces causing altered patterns in the trabeculae. One very interesting finding is with the lamina dura, which according to many observers is either lost completely or partly lost in

hyperparathyroidism making it an important diagnostic finding. Albright, Aub and Bauer (1934) found that only three out of the seventeen cases they studied showed absence of the lamina dura, and in some cases, bone decalcification was quite extensive. They also added that loss of the lamina dura was not pathognomonic of decalcification due to parathyroid disease. Albright, Sulkowitch, and Bloomberg (1937) emphasised that some patients with hyperparathyroidism have no clinical or radiographic evidence of the disease. Stafne and Austin (1938) described the osteoporosis, giant-cells tumours, cysts and changes in cortical bone, seen in dental radiographs of patients with hyperparathyroidism. Strock (1941) presented a summary of the dental findings in 45 selected patients with hyperparathyroidism, and in about half of these cases there was giant cell tumours of the jaws. The most consistant finding was the absence or partial loss of the lamina dura, and in the less severe cases, the lamina dura was merely extremely thin. Keating and Cook (1945) described thirteen cases of the 24 selected cases they studied of hyperparathyroidism, and found that in two cases there was complete loss of the lamina dura, and in the other eleven partial loss. Keating in a later report (1947) concluded that radiographs were useful in the recognition of even mild degrees of hyperparathyroid bone disease. Weinmann (1945) reported three cases of secondary hyperparathyroidism in which he found histologic changes in the bones of the jaws with no changes in the radiograph. Domeck et al (1958) re-emphasised this lack of correlation between the radiograph and histologic findings in sixteen cases. Cohn (1948) found that widening of the alveolar trabecular pattern giving it a bubble-like appearance was more characteristic of the disease than the loss of the lamina dura. Pugh (1952) claimed that subperiosteal resorption which he found in the phalanges, is manifested orally by the loss of the lamina dura but that, since this also occurs in other conditions such as Paget's disease and osteomalacia, it is not pathognomonic. He called attention to altered trabeculae, cystic lesions, and changes in the inferior dental canal, the mental foramen, the suture of the maxilla, and the antral floor. More recently many others have cited selected individual cases of hyperparathyroidism with loss of

lamina dura, and the occurrence of cysts in the jaws, and in some instances they were the first recognisable signs of the disease, Levy (1952), Coleman (1954), Koontx (1955), Tilman (1956), Bruce (1957), Brown (1958), Chaudry et al (1958), Cohen (1959), Sterling (1959), Attie and Blum (1960), Teng and Nathan (1960). Because these reports are mainly of selected cases, there is the danger of making generalisations of the diagnostic importance of dental radiographs in the detection of hyperparathyroidism. Because of this Silverman et al (1962) in an excellent report of 42 dentulous patients with hyperparathyroidism who were studied consecutively from the 77 surgically and histologically proved cases diagnosed at the University of California Medical Centre from (1956-1961), reviewed and examined the matter further. Only three showed typical hyperparathyroid dental changes (partial loss of lamina dura, giant cell tumours, and demineralisation). In two cases, dental films, following the removal of parathyroid tumours, showed healing of giant cell tumours, demonstrating a cause-and-effect relationship between adenoma and metabolic bone disease. They concluded that the loss of lamina dura and the appearance of giant cell tumours are late signs of hyperparathyroid bone disease which itself is a late complication of primary hyperparathyroidism.

Resch (1958) states that in his experience loss of the lamina dura is largly confined to those areas that were under the mechanical stress of abnormal mastication. Rosenberg and Guralnick (1962) however reviewed all proved cases reported at the Massachusetts General Hospital of hyperparathyroidism, totalling 220, and found the following changes in the lamina dura. There were 119 out of the 220 patients with bone disease; of the 67 who had classic bone disease (osteoporosis, cysts and marrow fibrosis) 32 were not examined for lamina dura. Of the 35 who were examined, the lamina dura was missing in 29 (83%), and present in the remaining six. No dental radiographs were taken of 23, of the 52 cases of mild bone disease (osteoporosis only). The lamina dura was absent in thirteen of those examined, (52%) and present in twelve. In 101 patients no bone disease was radiographical discernible. Among the 56 whose lamina dura was examined, five were absent (9%). They also found that ten of the 220 patients

had a giant cell tumour as the presenting symptom. They concluded that the absence of lamina dura is not an infallable sign of hypoparathyroidism, but is another aid in diagnosis and the presence of lamina dura does not rule out parathyroid disease, but the absence of the lamina dura around functioning teeth certainly demands further investigation.

These later two reports of Silverman et al (1962) and Rosenberg et al (1962) conflict somewhat in the incidence of lamina dura involvement in the disease in their cases and whilst I favour the detailed investigations made, particularly by Silverman et al there seems to be further clarification needed even yet.

Stafne (1952) points out that the radiographic evidence includes the disappearance also of the radiopaque lines of the lamina dura representing the borders of the maxilla sinuses, nasal fossae, alveolar crests and the wider crests of the inferior and lateral borders of the mandible. These changes occur when the disease is of a severe form and has existed over a long duration. Stafne (1952) also states that the roots of the teeth appear radiographically, "Spindle Shaped".

Burket (1957) states that extensive diffuse and nodular calcification can occur within the dental pulp.

Keating (1961) in a report of 395 surgically proved cases of hyperparathyroidism from the Mayo Clinic, states that subperiosteal resorption of the phalanges is the most underrated test and that its dental counterpart, absence of lamina dura, is the most overrated.

Whilst Keating's remarks seem true, the importance of the lamina dura as a diagnostic feature of the disease cannot be unduly minimised.

<u>Other changes in the jaws and teeth.</u>

The appearance of giant cell tumours in the jaws, loss of partial loss of lamina dura, and osteoporosis of the jaws, and the sharp contrast between the highly calcified teeth and poorly calcified bone has been considered under Radiographic findings.

Schour and Massler (1943) refer to the following changes in these structures;

1. The jaws become so depleted of calcium and soft that they can be moulded with the fingers.
2. A definite malocclusion occurs quite early, and in fact the first sign of the disease is often a sudden drifting of the teeth for no apparent reason (as occurs in diffuse alveolar atrophy). A definite spacing of the teeth with mandibular prognathism occurs.
3. The teeth are not loose (as in diffuse alveolar atrophy). This is a contradiction of what Borg (1935) stated that the teeth were loose but tightened on removal of the parathyroid tumour. Strock (1941) said that extraction of the teeth was difficult.
4. Caries, is rare, and if active before the onset of the disease appears to diminish during the course of the disease. Thoma and Goldman (1960) support this, that the teeth resist decay.

Thoma (1936) and Keating and Cook (1945) have reported evidence of root resorption, but expressed the opinion that it was attributed to pressure atrophy of the enlarging bone tumour and not to the disease itself.

In edentulous patients with the disease, the alveolar bases are poor for dentures, because of rapid resorption. The jaw bones can be so soft that sections can be removed by a scalpel, Southan (1959).

Cohn (1951) represented a case with recurrent masses in the mandible gingivae.

Occasionally the giant cell tumours may occur peripherally in the bone causing swelling of the jaws, Cohn (1952). Whereas every case of epulis is certainly not hyperparathyroidism, this diagnosis must be carefully considered in such a case, Albright and Reifenstein (1948).

Hyperparathyroidism is rarely seen in children, and when it does, changes in the structure of teeth occurs as seen in a case presented, by Thoma and Goldman (1960) of a fifteen year old boy with a epulis which proved to be due to hyperparathyroidism, which had extended over seven years. Pathologic examination of two premolars and a first molar removed from this boy, showed in the premolars contour lines made up of strips of densely staining dentine adjoining a strip of poorly calcified structure. In the pulp there are small cysts with vacuolisation of the odontoblastic

layer. In some places there was complete atrophy of the odontoblasts and tubular dentine was deposited. Pulp nodules and interstitial deposits of calcium were found. There was no evidence of any resorption within the tooth. Resorption was only apparent at the root surfaces where the roots contacted the giant cell tumours. The disturbance in dentine formation apparently took place during the active course of the hyperparathyroidism. There was no evidence of caries in the patients mouth.

Gardner et al (1963) state that another interesting point is that an increased salivary flow often accompanies the disease, which may bear on the reduced caries incidence.

These changes in the jaws in hyperparathyroidism are important because as Gardner et al (1963) point out, quite a few cases of the disease have been reported where only the jaws were noticeably affected, the rest of the skeleton being free at least of radiograph changes, Snapper (1949) and Levy (1952) etc. Lesions of many diseases frequently develop at points of irritation and trauma. The jaws are continually subjected to trauma, particularly if the teeth are present, which makes the jaws vulnerable and renders them a fertile diagnostic field. Cohn (1952) also makes this observation.

Histopathologic findings.

The chief change in the bone is evidenced by osteoclastic resorption which appears very active along the enlarged blood vessels in the Haversian system of the cortex and principally in the spongiosa, Thoma and Goldman (1960). Osteoclasts are seen in large numbers. Pick (1933) stated that one particular feature typical of generalised osteitis fibrosa is a "dissecting" of trabeculae by osteoclasts, the tendency they exhibit to cut through trabeculae. Hunter and Turnbull (1931), found that there was bone formation in almost all cases they examined, when sections were studied from the most severely affected parts. This is looked on by some as a process of repair rather than a feature of the disease, Schneider (1953). The structure of this new bone is quite different to normal bone, the lamelar arrangements being

replaced by a woven appearance, Kaufmann (1922). The woven bone is the course-fibred variety such as is found in the embryo; the fibres are interlaced and cellular lacunae are larger, more irregular and often confleunt; Apposition is accomplished by osteoblasts activated to repair the damaged bone. These cells are plumper than normal resting osteoblasts and have abundent granular oxyphilic cytoplasm. Often two or more rows of cells closely packed can be seen around the trabeculae indicating great cell. activity. Thoma and Goldman (1960). The resorptive process exceeds the deposition so that cement lines of bone apposition are missing, and there is little or no mosiac pattern present, Schneider (1953). Generally there is only slight evidence of new bone formation, Burket (1957).

Osteitis fibrosa which is a histologic sign for a number of diseases of which hyperparathyroidism is one, is due to replacement of the normal marrow by fibrous tissue, Schneider (1953). There is an increase in the supporting cells of the bone marrow, which it has been suggested, gives rise to osteoblasts and osteoclasts, which are both increased. It is not surprising therefore to find an increase in the parent cell-type, Albright and Reifenstein (1948). This fibrosis of the marrow is a conspicuous feature. A course network forms in the marrow spaces which connect the osteoclasts with the wall of the bone and replaces the trabeculae which are resorbed. There is also evidence of hyperaemia and oedema, which is seen not only in the marrow, but also on the pulps of the teeth. The vessels show evidence of thrombosis; some thrombi are new and contain brown pigment (haemosiderin), which is a characteristic feature of the osteoclastomas in hyperparathyroidism, which explains why they are sometimes called "brown tumours". Thoma and Goldman (1960).

Cysts are frequently seen but are not an essential part of the disease; they may be small, and barely visible with the microscope or they may be large enough to be seen in the X-Ray film. Weinmann (1945) state that these cysts are characterised by their lack of specific lining and Schneider (1953) commented that they are caused by degenerative changes. Hunter and Turnbull (1931) found that they were filled with an albuminous

fluid with or without red blood cells. These cysts may be a transitional stage of osteoclastomas.

Osteoclastomas are focal accumulations of foreign body giant cells of varying sizes. They are frequently found in the jaws, possibly due to the greater blood supply there, than in the long bones. Hunter (1931) believed that they are simply a response to excessive parathormone, causing complete resorption of the spongiosa. As the tumour increases in size, the cortex becomes involved, and the bone expands by periosteal opposition, but it may be completely destroyed. But the periosteum is never broken through. The osteoclastoma comprises therefore the benign giant cell tumour which has been reported to occur in multiple form. Microscopically they are identical with the solitary benign giant cell tumour consisting of a stroma of spindle cells with haemosiderin and numerous multinucleated giant cells. The haemosiderin is of a yellow-brown colour, occurring in granules and small masses and is produced from the endothelial leucocytes from haemoglobin. It occurs in the blood vessels containing thrombi or is distributed widely in the tumour tissue which gives the tumour the rusty brown colour and the name "brown tumour" The haemosiderin is disposed of by the giant cells which explains why there are so many of them present. Microscopically they are the same as in the solitary type of epulis occurring in the normal skeleton, except they contain more haemosiderin. Jaffe (1933), Thoma and Goldman (1960).

<u>Differential Diagnosis of Primary Hyperparathyroidism.</u>

This is very important because of the many diseases with simularities to hyperparathyroidism. A bone disease to be the result of hyperparathyroidism must be generalised. However, whereas the fundamental lesion, decalcification, in the case of hyperparathyroidism may be generalised, it is possible for secondary lesions, cysts and tumours to be localised. Under such conditions the superficial observer may have his attention called to the secondary lesions and miss the less conspicuous but more fundamental underlying generalised lesion. Metabolic diseases are generalised, which means the skeleton would be affected 100%. Albright and

and Reifenstein (1948).

Lisser and Escamilla (1962) give the following classification as to differential diagnosis involving the other conditions producing a hypercalcaemia, genitourinary tract disease and generalised and localised bone diseases.

A. Hypercalcaemia. (can result from a number of factors)

1. Steroid treatment of osteolytic metastasis from carcinoma of the breast; This can be ascertained by adequade history. Cortisone is effective in diminishing this type of hypercalcaemia. Mason and Warren (1931) studied metastatic carcinoma imitating hyperparathyroidism.

2. Multiple myeloma; Hypercalcaemia may occur. Differential points are that there is normal serum alkaline phosphatase with bone disease; increase in total blood protein; particularly globulin fraction; finding of plasma cells in marrow or blood; presence of, Bence Jones protein in urine much more common; electrophoretic pattern of serum proteins shows spike of abnormal globulin in gamma area. Albright and Reifenstein (1948) comment that this condition can be most difficult to differentiate from hyperparathyroidism, the X-ray picture being often very similar. Caylor and Nickel (1933) made observations of multiple myeloma simulating hyperparathyroidism.

3. Boeck's Sarcoidosis; serum phosphorus remains normal and total blood-protein is usually increased, particularly globulin fraction. The high calcium level is lowered by cortisone. Serum electorphoretic pattern shows characteristic increase of globulins.

4. Graves Disease.

5. Overtreatment with vitamin D(usually more than 1000,000 units daily); An adequate history should reveal this. This type of hypercalcaemia can be abolished by cortisone also. In hypercalcaemia in infancy it has suggested that a decreased rate of vitamin D inactivation us at fault; may have characteristic facies.

6. Milk-alkali (Burnett's Syndrome; shows hypercalcaemia without hypercalciuria and without change. It is caused by an excessive

intake of milk, resulting in renal insufficiency, azotemia, and occasional alkalosis.

7. Increased dietary intake of calcium-particularly in patients immobilized in casts.

B. Genitourinary tract disease;

8. Increased calcium in the urine and renal lithiasis can occur with increased dietary intake of calcium and alkali ((pseudohyperparathyroidism) particularly in immobilised patients and in multiple myeloma.

9. True diabetes insipidis may be suggested by the increased thirst but there is a negative Sulkowitch test and an absence of hypercalcaemia.

10. Chronic renal infection may produce nephrocalcinosis without hyperparathyroidism.

C. Bone Disease; with generalised changes;

11. Renal osteitis fibrosa generalisata (renal rickets) decalcification is generalised due to kidney disease. Differential points are that serum phosphorus is elevated; serum calcium is normal, low of only slightly elevated. Evidence of renal insufficiency with acidosis and elevated blood non-protein nitrogen; bone cysts less common. Secondary hyperplasia of the parathyroid gland may develop causing "secondary hyperparathyroidism".

12. Osteomalacia-generalised decalcification causing; deformities and bending of the long bones. Differential points are; normal or low serum calcium; pseudo fractures of the type described by Milkman, kidney disease found resulting in increased calcium excretion, conditions resulting from inadequate absorption of calcium, ie lack of vitamin D as in rickets. With rickets characteristic bone changes in regions of endochondral bone formation occurs. "Secondary hyperparathyroidism" may occur. Osteomalacia may be present also with both primary and secondary hyperparathyroidism.

13. Osteoporosis (postmenopausal and senile); manifested by generalised decalcification. Differential points are, normal levels of serum, calcium, phosphorus, and alkaline phosphatase,

lamina dura intact. Pathognomonic bone changes of hyperparathyroidism never present in the skull of hands.

14. Osteogenesis imperfecta-characterised by multiple fractures, beginning in infancy, patient may not survive. In later life differential points are; normal values for blood calcium; phosphorus and urinary calcium; intact lamina duraabout the teeth.

15. Fanconi (de Toni-Fanconi) syndrome-characterised by renal glycosuria, renal amino-aciduria, and renal phosphaturia, associated with hypophosphataemic rickets and osteomalacia. In infants, cystinosis is an important feature. This syndrome is a disorder of renal function sometimes familial and actually not an endocrinopathy.

D. <u>Bone Disease with localised changes;</u>

16. Polyostotic fibrous dysplasia (Albrights Disease)-cystic bone lesions may occur in segment distribution. Differential points are normal serum calcium and phosphorus, normal urinary calcium. The parathyroids may become hyperplastic. Brown pigment areas may occur with scattered edges on skin, is characteristic and in girls precocious puberty may occur.

17. Paget's Disease of bone (osteitis deformans); differentiated by typical radiographic changes (ie "cotton-wool" appearance of skull); normal levels of serum calcium and phosphorus. X-rays reveal characberistic secondary stage of new bone formation as well as destruction.

18. Multiple myeloma-both localised and generalised lesions may occur. The variations may show many characteristics of hyperparathyroidism(see 2.)

19. Metastatic malignancy-search for primary neoplasm important for differentiation; serum phosphorus is usually normal; does not lower TRP; cortisone decreases calcium.

20. Solitary bone cysts; usually occur at ends of long bones. Differential points are normal blood calcium, phosphorus, and alkaline phosphatase, and urinary calcium.

21. Boeck's sarcoidosis-manifested by localised bone lesions; suggestive of chemical changes (see 3)

22. Epulis-tumour of alveolar process, usually a fibroma or giant-cell sarcoma. Hyperparathyroidism must be considered. Differential points are blood chemical levels are normal, and urinary calcium is normal. Lisser and Escamilla. (1962).

Albright and Reifenstein (1948) state that lymphoma, benign metastasizing haemangeoma, Gaucher's Disease, histiocytosis, chronic radium poisoning and renal osteitis fibrosa generalisata all might be occasionally mistaken for osteitis fibrosa generalisata.

According to Burket (1957) the oral findings particularly those of the jaw bones might be differentiated from Paget's Disease, multiple myeloma, and ameloblastoma and osteomalacia. Ameloblastomas are rarely bilateral and usually involve the mandible. The radiographic findings, and may be biopsy, may be needed to differentiate it from fibrous dysplasia.

Keating in his excellent article of (1947) commented that hyperparathyroidism should be considered.

1. In all cases of cystic demineralisation of bone,
2. In all cases of renal calculi or renal insufficiency of undetermined origon.
3. In all cases of unexplained polyuria and polydipsia, and
4. In all cases of severe and unexplained gastro-intestinal symptoms.

Treatment.

Lisser and Escamilla (1962) list the following;

1. Surgical removal of the parathyroid adenoma, or resection of all but about 200mg. of hyperplastic parathyroid tissue. The tumour is often difficult to find and it may be necessary to explore the posterior mediastinum (readily accessable through a cervical incision, sternum splitting being rarely necessary) multiple tumours may also be present. Even when diagnosis rests solely on blood chemistry abnormalities, surgical excision should be attempted. The occurrence of post-operative tetany, particularly if the bone is involved, signifies successful removal, but it requires replacement therapy in a suportive way of intravenous calcium gluconate, parathyroid extract (10-100 units daily) later vitamin D (50,000-150,000 units daily) until urine Sulkowitch test shows a 2+ reaction.

2. Irradiation of the parathyroids is rarely helpful.
3. Parathyroid Crisis, due to acute hypercalcaemia, high calcium intake as in ulcer regimen may precipitate it. Prompt emergency therapy is mandatory to save life and consists of hydration and restoration of fluid and electrolyte balances, followed by surgical extirpation of the adenoma as soon as the condition of the patient permits.
4. "Secondary hyperparathyroidism" is rarely benefited by subtotal parathyroidectomy.

Archer (1961) adds that no oral surgery is indicated. The osteolytic lesions will be gradually filled in with the new bone, following the parathyroidectomy.

Most authors agree that surgical intevention is the only satisfactory way to treat this disease. A high calcium intake can prevent the negative calcium balance and can even produce a strongly positive one, but it is the kidney complications, which are serious and irreversible, that necessitate surgical treatment.

Prognosis.

The disease tends to be chronic, lasting many years, but if unrecognised and untreated, leads to fatal complications, these may be prolonged hypercalcaemia accompanied by muscular weakness, nausea, vomoting, depletion of the electrolytes, and dehydration but more frequently renal failure from progressive nephrocalcinosis or pyelonephritis.

Prognosis is good especially if surgical intervention before renal complications become irreversible. Spontaneous remission following infarcation of the parathyroid adenoma has been reported Lisser and Escamilla (1962).

Chaudhry, Hayes and Gorlin (1958) comment that renal insufficiency may be progressive in spite of the cure of the hyperparathyroidism.

Prompt adjustment of serum calcium and phosphorus levels following surgery is essential. Tetany is the danger following surgery, especially where osteitis fibrosa generalisata renal damage complicates the disease, Albright and Reifenstein (1948). This is due to insulation of the bone with osteoblasts from the body fluids, and it cannot give up its calcium and phosphorus intake. Hence the patient should be on a high calcium, low phosphorus regimen. In time the bone adjust themselves and the hypocalcaemia

and tetany disappears. The end state of the skeleton lesions is not normal bone, at least not for some five years, (Schneider (1953). A very dense skeleton results, for instance as seen in the skull, instead of the two cortical plates with diploe in between, there is a solid mass of bone formed, Albright and Reifenstein (1948).

Tillman (1956), studied a patient post-operatively over a period of four and a half years, and found the reformation of bone trabeculae and lamina dura around the teeth.

SECONDARY HYPERPARATHYROIDISM.

Is a condition where, because of some modifying circumstances, more parathyroid hormone is needed by the body than under normal circumstances. The condition probably occurs under the following circumstances;

1. Calcium deprivation due to diet,
2. Pregnancy.
3. Lactation,
4. Rickets and osteomalacia,
5. Chronic nephritis. Albright and Reifenstein (1948).

Histologically, one finds a hyperplasia of the parathyroid glands. Clinically the condition reaches its most marked degree in cases of long standing chronic renal insufficiency. Castleman and Mallory (1935) described the histologic characteristics, as follows;

1. A decrease or absence of intercellular fat tissue,
2. A predominence of normally sized chief cells.
3. An absence of mitosis.
4. More numerous oxyphil cells that one would expect for the age of the patient.
5. A somewhat higher glycogen content of the cells that one would expect in adenomata or in hypertrophy of the parathyroid tissue.

It should be noted that a hyperplastic gland, whilst it may not be any larger than the normal gland, is producing more hormone because the fat cells are replaced by epithelial cells.

Keating (1947) states the secondary hyperparathyroidism is a compensatory and probably essential adjustment of the body to the effects of some other primary condition. It should not therefore be treated surgically. A remarkable effective regimen has been devised for improving the chemical and skeletal status of patients who have renal osteitis and renal rickets. This does not unfortunately modify the course of improve the outlook of the underlying renal disease.

Domeck et al (1958) observed lesions in the maxilla in secondary hyperparathyroidism.

EXPERIMENTAL HYPERPARATHYROIDISM.

The injection of parathormone daily into guinea pigs produced changes similar to those found in generalised osteitis fibrosa, except that bone apposition is not affected. Jaffe, Bodansky and Blair (1930).

Elsworth and Futcher (1935), in nephrectomised dogs were able to demonstrate a rise in calcium in the blood following parathyroid hormone injections. Collip, Pugsley, Selye and Thompson (1934) and McJunkin, Tweedy and McNamara (1937) were able to produce bone changes in nephrectomised animals with parathyroid hormone. Ingolls, Donaldson and Albright (1934) repeated and extended these observations and demonstrated that parathyroid hormone does not have a direct decalcifying effect on bone, even in the absence of the kidneys and that this effect is independent of the acidosis produced by nephrectomy and of the parathyroid hormone extract.

Calcification of the Dentine;

Schour, Tweedy and McJunkin (1934) found that in the teeth of rats, the primary effect of one injection of parathormone, which causes a temporary rise in the serum calcium level, is as follows;

1. At the original junction of the dentine and predentine at the time of injection a hypermineralised line staining darkly with haemotoxylin, which they define as the "calciotraumatic line".
2. A hypomineralised layer, demonstrated by its easy absorption of eosin stain, in contradistinction to ordinary dentine which absorbes the basic stain. The layer is the average width of the predentine.
3. A secondary reaction immediately follows as the calcium level returns to normal, characterised by a corresponding hyperminerealisation of the next trip of dentine which is darkly staining with haemotoxylin.

Irving, Weinmann, Schour and Tweedy (1949) later found in addition, that the rate of dentine formation is reduced.

Calcification and Resorption of bone;

Schour, Tweedy and McJunkin (1934) found that the alveolar

bone of rats treated with parathormone, shows an abnormal increase in osteoblasts and in addition a fibrous change in the bone marrow, presenting as well the characteristic changes of osteitis fibrosa in the long bone. It should be noted that whilst the alveolar bone is almost wholly resorbed, the enamel and dentine remain unaffected. In fact the dentine forming and calcifying during the experiment appears on the whole to be hypercalcified. The changes are of special interest because they reveal in a striking manner, the physiological differences between enamel and dentine, on the one hand, and the bone on the other, Schour and Massler (1943).

In prolonged hyperparathyroidism in rats, Burrows (1938), found that there is a change in the alveolar bone of molars from a spongy to an almost compact structure. Mortimer (1937) however found that this effect is quite different from that seen in acute hyperparathyroidism, in which a marked osteoporosis occurs.

Schour and Massler (1943) comment that in view of the conclusive findings that enamel and dentine unlike bone, do not show resorption in hyperparathyroidism, it is surprising that, in the literature, statements persist that the teeth are decaleified in hyperparathyroidism. The teeth may become loose as a result of the active resorption of the alveolar bone, but the teeth themselves remain well calcified. Growth perse and the eruption of the teeth do not seem to be disturbed.

Munson (1956) states that the injection of parathyroid extract, which is followed by increased concentration of calcium in the blood need not result in uniform hypercalcification. The initial elevation of the level of calcium in the blood is the result of mobilisation of calcium from the skeleton, and this is likely to be associated with a period of deficient calcification. When the injected hormone has been dissipated, a period of hypercalcification may be expected to follow and to persist as long as the level of calcium remains sufficiently high to inhibit the secretion of the parathyroid hormone.

Fig. 18.

Hyperparathyroidism. Osteitis fibrosa cystica showing up in giant cell tumours of the maxilla and forehead. Colby, Kerr, and Robinson (1961).

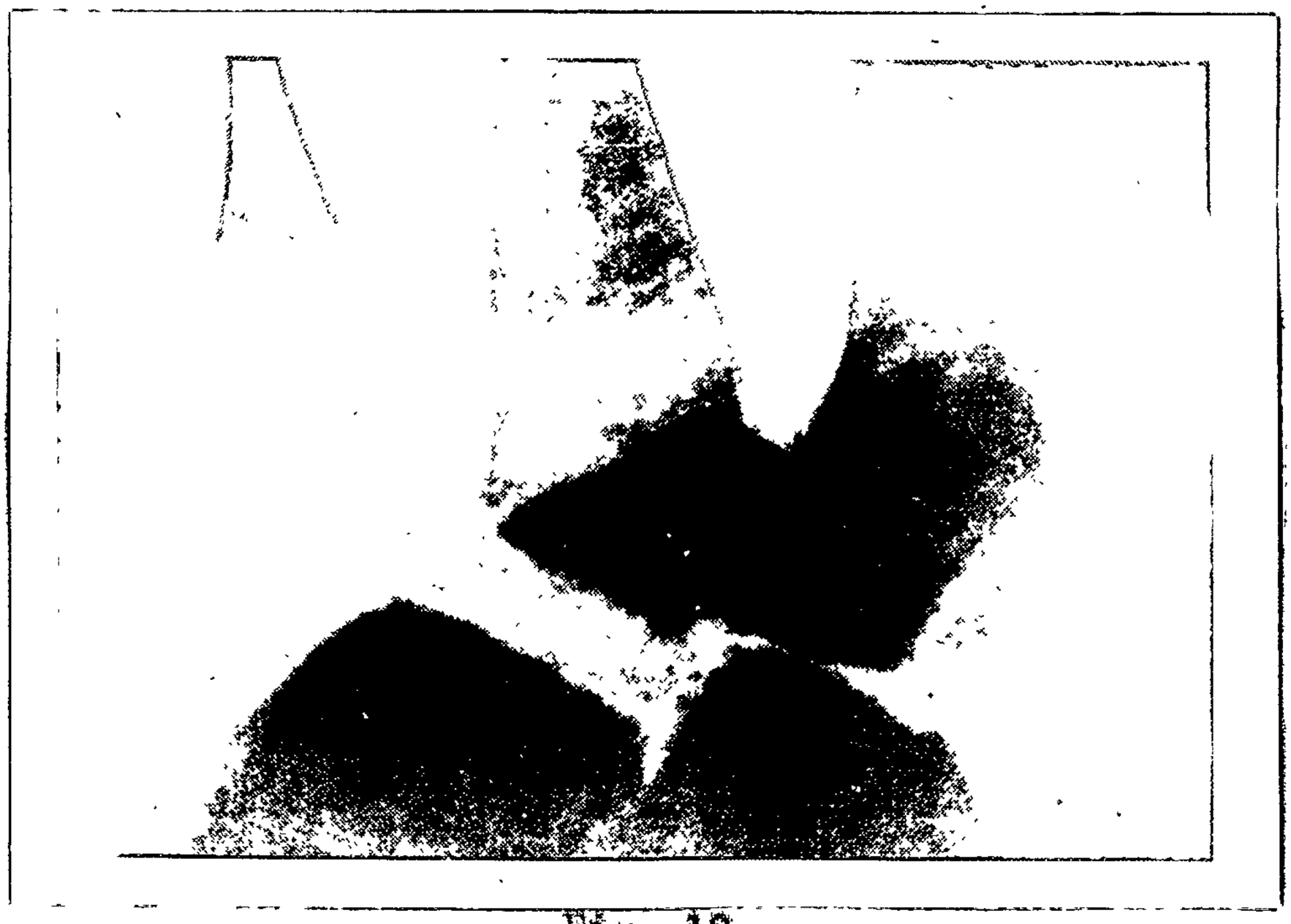

Fig. 19.

Hyperparathyroidism. Radiograph showing giant cell tumour and partial loss of lamina dura.
Colby, Kerr and Robinson, (1961).

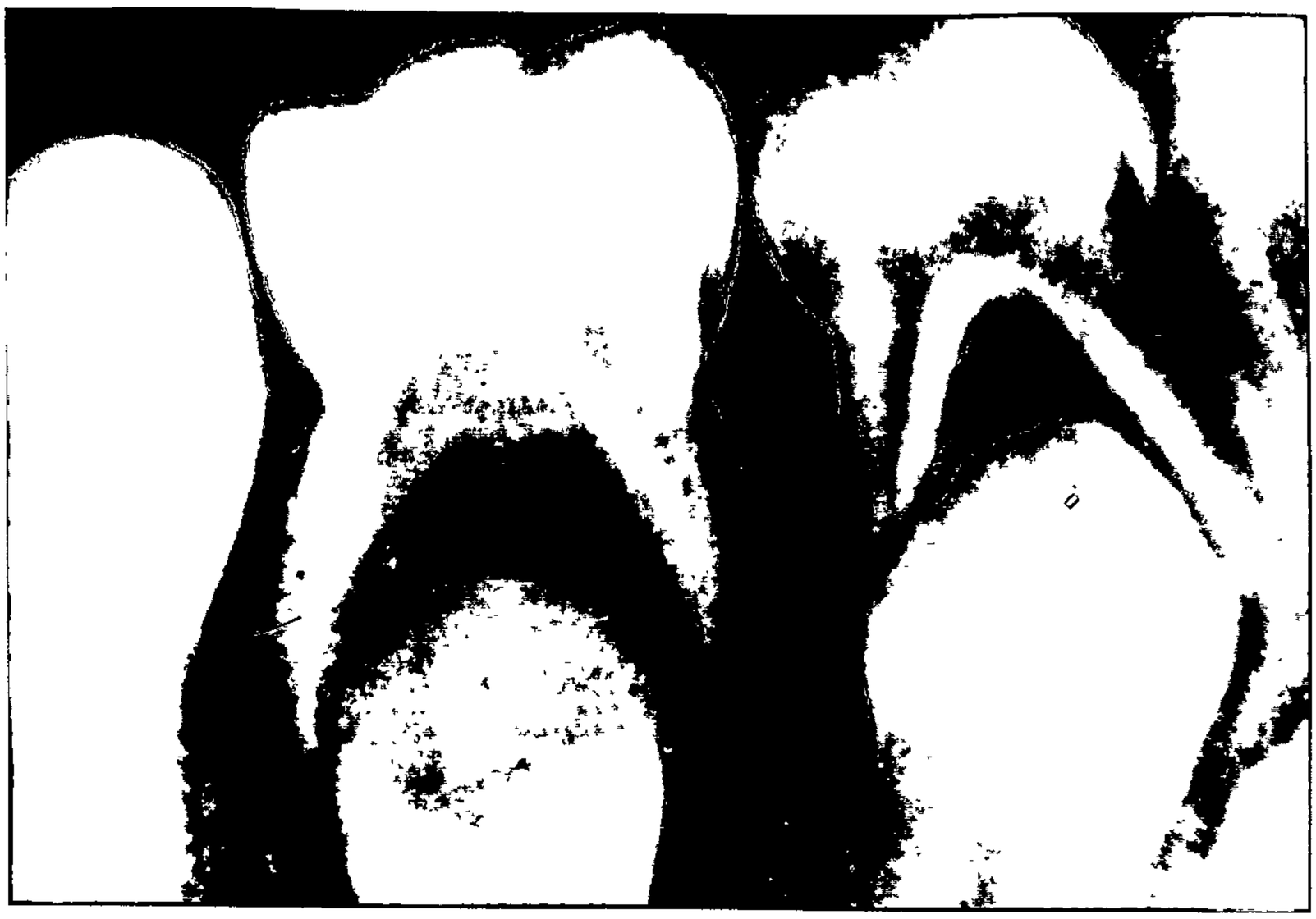

Fig. 20.

Hyperparathyroidism. Radiograph showing absence of the lamina dura, and a "ground-glass" appearance of the bone. Shafer, Hine, and Levy (1963).

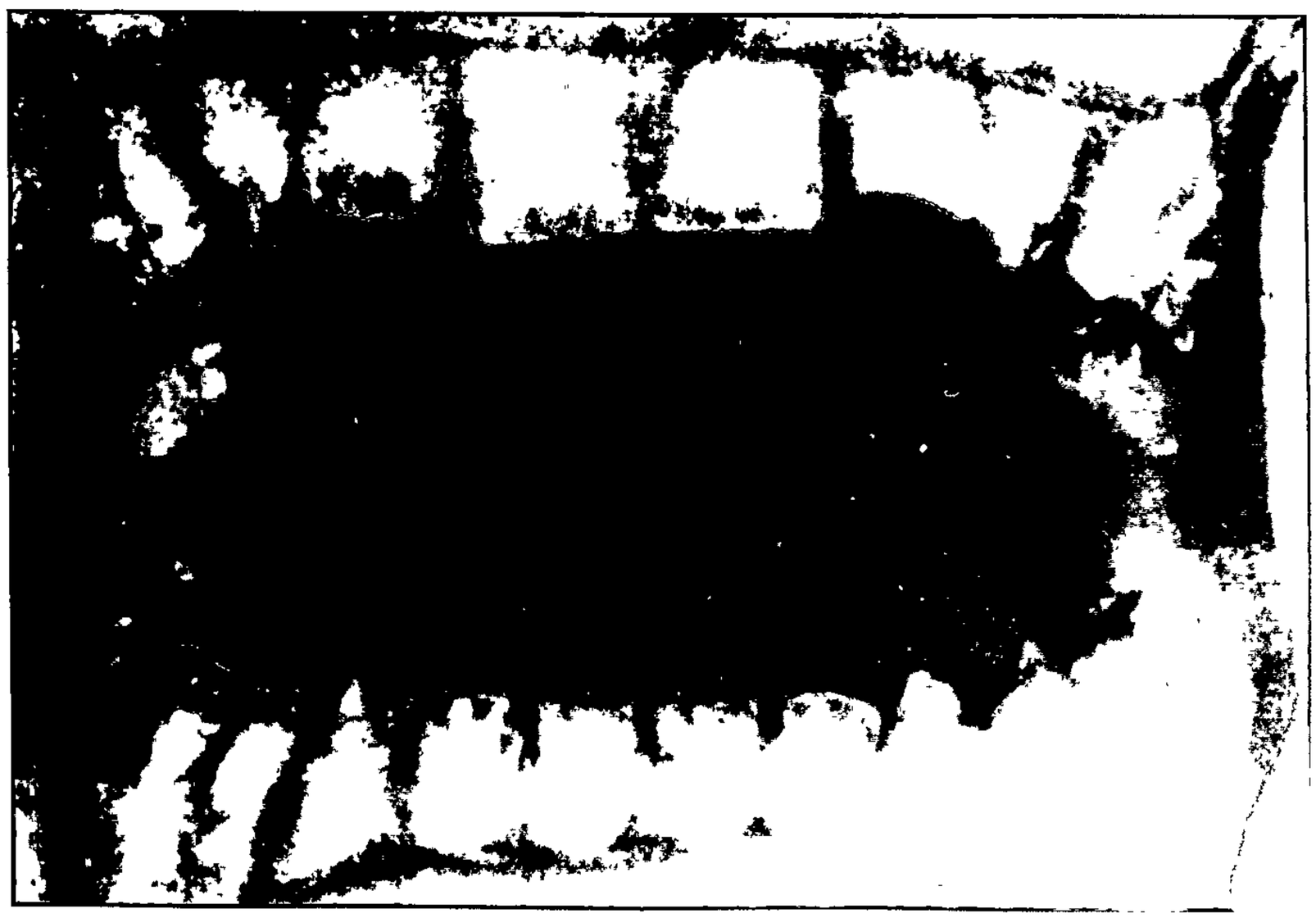

Fig. 21.

Hypoparathyroidism. Radiograph demonstrating enamel hypoplasia in a patient who had the disease in infancy. Shafer, Hine, and Levy(1963).

HYPOPARATHYROIDISM, (PARATHYROID TETANY)

Clark and Keli in (1815) and (1816) respectively, have short accounts of tetany, while Dance (1831) described a case of tetany in which were the carpopedal spasm, convulsions, and sharp piercing cries of the patient. No definite name was given to this condition and its aetiology was not suspected.

In (1874) Erb, by electrical stimulation of the motor nerves, noticed the neuromuscular hyperexcitability characteristic of tetany (Erb's sign). Chvosteck, two years later described, the facial contractions that occur when percussing over the zygoma, (Chvosteck's sign). Corvisart (1852) applied the name tetany to this syndrome, just some 28 years before the parathyroid glands were discovered. In (1880) Weiss noted the occurrence of tetany after the complete removal of the thyroids, but was unaware of the existance of the parathyroids. The parathyroids were discovered by Sandstrom of Sweden, and Barber of England (1880-81), but they were not aware of their function.

Gley (1891) believed that the parathyroids had a function apart from the thyroid gland, and that the occasional occurrence of tetany after thyroidectomy, might be due to extirpation of the parathyroids.

Kohn (1895) established their embroyological, anatomical and functional independence from the thyroid gland, and Vassale and Generali (1900) demonstrated that complete parathyroidectomy caused tetanic convulsions and death, while when one parathyroid was left, tetany did not occur.

A hypofunction of the parathyroid glands result in a marked hypocalcaemia with resultant increased excitability of the nervous system (parathyroprivivtetany). It should be remembered however that tetany is due primarily to the hypocalcaemia and that the latter may be caused by not only a deficiency of the parathyroid hormone, but also be due to an alkalosis of failure in the absorption of calcium due to a deficiency of calcium and phosphorus in the diet, an overabundance of phosphorus or a deficiency in vitamin D, Wolf (1939).

Aetiology;

1. The commonest cause of hypoparathyroidism is the accidental removal or damage done to the parathyroid glands in the course of a thyroid operation. Not infrequently the malady when thus produced is transient, the damaged glands regenerating after several months, Albright and Reifenstein (1948). Thoma and Goldman (1960). state that since, there are usually accessory glands, complete ablation is rare.

2. Very rarely hypoparathyroidism occurs idiopathically, Drake, Albright, Bauer, and Castleman (1939). They found on autopsy, of one of their cases a normally gross appearance of the glands, but microscopically the epithelial cells were replaced, by fat cells. Albright and Reifenstein (1948) do not believe this is due to any anterior pituitary trophic action. Sutphin, Albright and McCune (1943) reported five cases of idiopathic hypoparathyroidism associated with moniliasis, three of the five cases occurring in siblings. Talbot, Butler and Maclachlan (1943) had previously reported two cases of moniliasis associated with Addison's Disease, in one of whom hypoparathyroidism. There seems to be a definite tendency for idiopathic hyperparathyroidism to be associated with Addison's Disease, which was demonstrated by Leonard in (1946) in a case presented.

Lisser and Escamilla(1962) reported that up to (1952), 52 cases of idiopathic hypoparathyroidism had been described.

3. There is a considerable evidence that the parathyroid glands may be deficient functionally, shortly after birth and that convulsions in such infants may be a manifestation of a hypoparathyroidism, Bakwin (1939). Of considerable academic interest, is a case reported in which hypoparathyroidism developed in a child born of a hyperparathyroid mother, Fridersichsen, (1939). The inference is that the infant's parathyroids became compensatorily atrophied in intrauterine life. Van Arsde (1955) reported a similar case. Goldman et al (1952) reported a case of juvenile hypoparathyroidism.

Thoma and Goldman (1960) state that congenital hypoparathyroidism is rare. Stones (1954) comments that infantile tetany usually occurs between the ages of six months and two years, and is due to the parathyroid gland not having started to function properly,

at this early age.

Lisser and Escamilla (1962) state that hypoparathyroidism can occur at any age. In addition to stating the aetiology already referred to, they add that it can also be caused by abnormal increased calcium loss during lactation, and is frequently associated with rickets in infancy of childhood.

Symptoms and Signs;

Lisser and Escamilla (1962) lists the following;

1. "Tetany of the newborn" (may be transient)

(a) Laryngeal spasm or bronchospasm, causing loud respiratory crow but suffocation is a rare complication.

(b) Carpopedal spasm-flexing of the hands at the wrist and the extension of the fingers and thumbs, and turning down of the toes, with a high arching of the soles.

2. Postoperative hypoparathyroidism-formerly common, but now less frequent but may occur even in competant hands of an expert goitre surgeon, it is more likely when there is fewer than four parathyroids or after a second or third thyroidectomy when normal landmarks have been obliterated; it is usually evident 1-2 days postoperatively; it has rarely been precipitated by an abrupt surgical menopause many years after thyroidectomy. The severity of it is as follows;

(a) Latent tetany-parathesias of the extremities or numbness or stifness around the mouth may be the only symptoms; when moderately severe, muscular fibrillary twitchings and crampings occur.

(b) Manifest tetany-true tetanic spasms, most frequent in hands and feet; in childhood it can simulate epileptiform type of convulsive attacks; it can occur with acute changes in serum calcium concentration.

(c) Diminished vision-"tetanic cataracts" may develop fairly soon after accidental parathyroidectomy. They are usually bilateral and may advance in spite of treatment. Fine opaque granules then later diffuse opacities appear beneath anterior and posterior lens capsules.

3. Chronic idiopathic tetany-additional symptoms are;

(a) Trophic changes-thinning and loss of hair, brittleness and loss of nails; punctate enamel defects in the teeth; thick and rough skin.

(b) Severe headaches, mental retardation, and psychiatric disturbances irreversible if result from cerebral calcification, but curable if caused by hypocalcaemia.

(c)Other symptoms-spasm of occular muscles; tachycardia and irregular rythms; "gastric tetany", with associated pain, cramps, nausea, vomiting suggesting intra-abdominal disease.

(d) Metastatic calcification appear in the soft tissues

(e) Ocular fundi-may show papilledema associated with increased intracranial pressure which has been confused with brain tumours.

(f) Extrapyremidal dyskinesias, such as hypertonicity and choreiform movements.

(g) Dental changes-enamel defect and yellow spots, transverse furrows and horizontal grooves and punctated holes, blunting of the roots, occur if tetany is active during tooth development. (see below) .

Important diagnostic signs;

Chvostek's Sign (1876) most characteristic; unilateral contraction of the superficial muscles of the upper lip elicited by tapping the facial nerve in front of the ear; eyelids jerked laterally indicate a strongly positive test. Albright and Reifenstein (1948) describe three degrees of this sign.

2, Trousseau's sign-production of carpal spasm, causing flexing of the wrist and metacarphalangeal joints, extension of the fingers and adduction of the thumb to the index finger (accoucheur's hand), with some pronation of the forearm; elicited by temporarily interrupting the circulation of the forearm by pumping up the pressure in the blood pressure cuff; in severe cases, constriction of or only a few seconds initiates spasm; in milder cases pressure occlusion for 2-5 minutes may be necessary.

3. Erb's sign (1874) heightened irritability of muscle by stimulatioh with a galvanic current; special apparatus is necessary and it is seldom used nowadays. Lisser and Escamilla (1962).

Laboratory findings.

Lisser and Escamilla (1962) list the following Blood and urinary chemistry findings;

1. Blood serum calcium is low. (between 4-8mg%; normal is 9-11mg%)
2. Total blood proteins - should be checked and if low, less circulating calcium is bound as calcium proteinate, leaving more available as ionizable calcium; thus, a low total serum calcium may not always cause tetany.
3. Blood serum phosphorus is elevated usually to 4-12mg% (normal is 3-4mg% in adults and 3mg% in children); if it is high, tetany is likely despite only moderate depression of serum calcium.
4. Urine Sulkowitch Test (see "Laboratory findings" under hyperparathyroidism) is negative of only slightly positive-0-1+ reaction (normal is 1-2+); it can be used as a gauge for therapy, (fasting urine specimen desirable)
5. Ellsworth-Howard test, shows an increased excretion of phosphorus in the urine after the injection of 2mls of parathyroid extract. This differentiates pseudohypoparathyroidism.

Radiographic findings;

Bone may appear as mildly dense. And there may be metastatic calcification apparent in the soft tissues, particularly in the choroid plexus or basal ganglion, predominately in the caudate and globus pallidus; to a slighter extent in the putamen and dentate nuclei. There is usually no correlation between the clinical picture and the degree of calcification. Dental radiographs may show enamel defects and blunting of the dental roots. Lisser and Escamilla (1962). Sunde and Hals (1961) also report a case with similar dental radiographic findings.

Munson (1956) states that hypoparathyroidism and the associated low blood calcium does not inevitablu produce hypocalcification. In long term studies, there has certainly not been abnormality as one might expect from the low calcium level of the blood. Hypoparathyroidism brings into play two opposing mechanisms; one that tends to calcify - the absence of the calcium mobilising hormone of the parathyroids.

Keating (1947) found that in actual fact, there was a slight

increase in the density of the bone in hypoparathyroidism, which is also supported by Albright and Reifenstein (1948)

Cranio facial Development.

Cranio-facial development is normal, although there may be an underdevelopment of the pre-maxilla and open-bite with hypoplasia of the teeth. Thoma and Goldman (1960).

Dental changes.

Several workers have observed that the teeth may be affected when tetany occurs during the period of formation.

Fleischmann (1908) was the first to show that rachitic tetany could cause hypoplasia of the enamel. Albright and Strock (1933) confirmed and extended these observations and found that subjects that had parathyroid insufficieney occurring during childhood, might show hypoplasia, aplasia and various other defects of enamel. Resch (1958) reports a case of four children born to a hypoparathyroid mother but showed no dramatic dental defects. However, there appeared to be an increase in caries.

Humphreys (1939) was the first apparently to describe the histological changes in the teeth resulting from this disease. He reported a typical case of a woman who had suffered from parathyroprivic tetany since the age of twelve. The dentine forming and calcifying during the parathyroprivic period showed changes similar to those seen in the dentine of parathyroidectomised rats (see later). The incremental stratification was accentuated and showed alternate disturbances in apposition. On the other hand, Humphreys (in a personal communication to Schour and Massler (1943) found no changes in the teeth of a patiant whose parathyroids were accidentally removed in thyroidectomy at the age of 23. These negative findings again show that disturbances in calcium metabolism to which growing and calcifying dentine responds with remarkable sensitivity will not affecg the dentine that was formed and calcified previous to the disturbances;

Schour and Massler (1943) referred to a case with open-bite and hyperplasia. They state the open bite in the anterior region occurs if hypoplasia is present.

Keating (1947) reports a case of spontaneous parathyroid insufficiency in two sister, the younger, fifteen years of age, having had symptoms of severe tetany since three years, and amelogenesis had appeared to have been unaltered up to the age of three years, but after that time all the teeth had had enamel formed since that time showed enamel defects, and several teeth were unerupted and these appeared devoid of enamel. The older sister of 28 years of age, also had a history of tetany beginning since early childhood, but since the symptoms were milder, the time of onset could not be ascertained accurately. There appeared a decreased amount of enamel over the surfaces of all the teeth, and enamel seemed entirely lacking on the unerupted but unimpacted third molars. Other members of the family were examined and were found to have normal parathyroid function and normal teeth.

Kronfeld, (1955) pointed out that all these changes in the teeth, were the direct result of the lowered calcium level in the serum.

Resch (1947) found that hypoparathyroidism of long standing had no effect on the teeth which were developed. The dental caries index was not increased. Children born during the period of tetany readily developed caries of the deciduous teeth, which resulted in malocclusion and altered jaw development.

There has been further literature on human subjects showing dental changes in hypoparathyroidism. A survey is presented by Hanstead and Holst (1952), who also present a case of their own. Reports are also given by Steinberg and Waldron (1952), Nally and Courvoisier (1953), and Hagberg and Olsson (1956). The following symptoms have been described; delayed tooth eruption, multiple retention of the teeth, root resorption, severe enamel hypoplasia, and aplasia. Abnormalities in mineralisation occur only in areas which are mineralised after the onset of the disease. It has been emphasised that disturbances in tooth eruption are symptoms of considerable importance in regard to early diagnosis of this rare disease. Hinricus (1956) reports five cases in which the onset of the disease occurred at different ages. He states that both the tooth matrix as well as final calcification are affected. The enamel is appreciably affected only if the disease has its onset

before enamel formation. He found some evidence of delay in tooth eruption. Early diagnosis and proper treatment will prevent permanent damage.

Sundo and Hals (1961) carefully studied the dental changes in a girl who for more than sixteen years suffered from hypoparathyroidism, beginning at fifteen months, when tetanic convulsions began occurring. They state that usually enamel hypoplasia is the only dental anomaly mentioned in connection with the disease in man, the reason undoubtedly being due to lack of histological study of earlier cases. They found that the changes in the dentine were far more profound than in the enamel, exhibiting themselves as a gradual loss of the properties of specialisation on the part of the dentine forming cells with the result, that there is a gradual transition between dentine and a bone like tissue at the root end of the tooth. The complete arrest of the development of the roots of the teeth at the age of nine and a half years, is for the most part caused by the changes in the dentine. A bone lamella terminates in the pulp chamber. The pulp tissue is normal except where it is infected from the pathological processes. The cementum is normal. Eruption was delayed considerably and at the age of eleven, her dental picture was that of a normal child of seven years. They found a definite relationship between the dental changes, and the onset of the disease. Gardner et al (1963) support these findings.

Gardner, Breen and Zaharin (1963) add that one other change that is seen in parathyroid hormone deprivation is a thickening of the alveolar bone. The parathyroid hormone tends to control to a great extent, the breaking down process of bone, and if not present, this normal osteoclastic activity is rarely seen in the jaws and then only in cases in which hypoparathyroidism has existed for many years.

Differential Diagnosis

Other conditions which cause tetany may be confused with hypoparathyroidism. The two causes of tetany are hypocalcaemia and alkalosis. Albright and Reifenstein (1948) state that as far as they are aware, there is no convincing evidence that

tetany from alkalosis is entirely due to some secondary changes in the availability of calcium ions.

Lisser and Escamilla (1962) lists the following for differential diagnosis;

1. Tetany from inadequate intake of absorption of calcium. Found in rickets, osteomalacia and steatorrhoea. Rickets and osteomalacia are differentiated by normal or slightly low serum phosphorus; steatorrhoea is indicated by excessive fat in the stools, and the recognition of latent steatorrhoea may require a fat tolerance test.

2. Alkalosis. May result in localised or generalised attacks of tetany; it can also result from hyperventilation, vomiting, or excessive intake of alkalies. It is differentiated by having normal serum calcium, and phosphorus levels and a normal urine Sulkowitch reaction. Inducing hyperventillation will provoke an attack.

3. Increased serum phosphorus, may cause tetany and can occur in renal insufficiency and poisoning with oxalate or citrate ions, and with magnesium deprivation. Differential points are urinary evidence of kidney disease and elevated blood NPR.

4. Pseudohypoparathyroidism. (Sebright-Bantam syndrome). Parathyroid hormone production is normal, but the end organs fail to respond, but incidence is rare. Patients are short and thick set, have round faces, and brachydactylia with short matacarpals. The Elsworth Howard test differentiates, which measures hourly the excretion of phosphorus in the urine three hours before and 3-5 hours after intravenous injection of 2mls (200 USP. units) of parathyroid extract. In true hypoparathyroidism urinary phosphorus excretion may be increased tenfold but in pseudohypoparathyroidism it remains normal or at most doubles.

5. Pseudo-pseudohypoparathyroidism. The usual anatomical stigmate of pseudohypoparathyroidism is present, but serum calcium and phosphorus levels are normal; there is no clinical evidence of hypoparathyroidism, and the Ellsworth Howard test is normal.

6. Other differentiations must include;

a) Epilepsy-electroencephalogram with intravenous injection of calcium during the tracing may be required to distinguish the

two conditions.

b) Asthma-suggested by characteristic stridor.

c) Arthritis-suggested by muscular spasm.

d) Psychic disorders-the anxiety may be especially confusing, a low serum calcium provides strong evidence of hypoparathyroidism.

Treatment.

The treatment of hypoparathyroidism is concerned mainly with the raising of the serum calcium level. This may be done with a diet high in calcium and low in phosphorus, by introduction of calcium gluconate, by the production of a mild acidosis, by subcutaneous injections of parathyroid extract, by the use of dihydrotachysterol (a derivative of ergosterol), and vitamin D. Garnder et al (1963), Lisser and Escamilla (1962) list the following; details for the treatment of acute and chronic hypoparathyroidism;

Acute Tetany;

1. Intravenous calcium is the most satisfactory in the form of ten mls of 10% calcium gluconate. It can be repeated if necessary be, extravasation must be avoided.

2. Sedatives to control nervous tension, are useful.

3. Parathyroid extract is useful in early post-operative tetany, (10-100 units U.S.P daily parenterally in single or divided doses) the effect is apparent in about four hours and last about twenty four hours. Antihormone formation occurs after about 7-10 days treatment and a change to another drug is desirable.

Chronic hypoparathyroidism;

1. Dihydrotachysterol (A.T. 10) is very valuable. Starting dose is 1-3ml or 2-6 capsules (each 0.625mg) orally daily until the Sulkowitch test becomes moderately positive, then diminish to maintenence dose of 0.25 to 0.5ml daily Cortisone should be avoided as it nullifies the calcium raising effects of A.T.10. A.T. 10. is moderately expensive.

2. Vitamin D-is less expensive and generally satisfactory and acts by increasing the intestinal absorption of calcium and phosphorus. It is important if possible to fix phosphorus in the intestinal tract with aluminium hydroxide. Dosage is 50,000 unit capsules (vitamin

D or D2-calciferol) one to three daily. Much larger doses may be required but overdosage is to be watched. The Sulkowitch test is to be kept at 2-3+. Intravenous injection of Vitamin D has been reported successful when oral administration of A.T 10 or vitamin D is unsuccessful, Bernstein and Moore (1959) also in such refractory cases magnesium sulphate administration has been reported helpful, as four gms three times daily. Howe (1961).

3. Aluminium hydroxine (fixes phosphorus in the intestinal tract) in a dosage of one to three tablespoons after meals.

4. Calcium (gluconate, lactate, or chloride) can be given orally, but avoid combination with the phosphate ion. Usual dosage of calcium gluconate or lactate is 4gm, three to six times daily in fruit juice or water or sprinkled on the food. Calcium chloride occasionally causes gastrointestinal irritation - dosage is one 10 mls of a 30% soln, three times daily in water after meals.

5. Dietary and modification to limit intake of phosphate ion, by the avoidance of dairy products. In severe cases/the phosphate ion intake should be limited to 0.3-0.5mg daily.

6. Dessicated thyroid is important if hypothyroidism is also present, but helpful even in euthyroid patients, as it aids the absorption of calcium from the intestinal tract. Dosage is 1-2 grains daily

8. Strontium is occasionally helpful.

9. Transplant of foetal parathyroid tissue or adenoma from a case of hyperparathyroidism after preparation in tissue culture occasionally provides prolonged substituition, Escamilla et al (1957)

Lisser and Escamilla (1962) give a detailed typical regimen for a patient with moderately severe hypoparathyroidism.

They also state that the aim of treatment is to prevent tetany, but keeping the serum calcium at 8mg% or above and serum phosphorus 5mg or below. Female patients undergo pregnancy fairly well, but lactation should be surpressed.

Prognosis.

Is good if the chemical changes are adequately controlled. Improvement occasionally occurs spontaneously if postoperative oedema and haemorrhage in or around the parathyroids become absorbed.

If severe and untreated, metastatic calcification, particularly in the brain can cause irreparable mental deterioration. Calcifications can also occur in the periarticular tissues, lungs, blood vessels, hearts, and gastrointestinal tract. Spinal fluid pressure increases and papilledema may occur. Tetany cataracts usually fail to diminish despite of the above therapy, and eventually require surgical extirpation, Lisser and Escamilla (1962).

PSEUDOHYPOPARATHYROIDISM.

This interesting syndrome was described by Albright, Burnett, Smith and Parsons (1942)/and has essentially the same symptomatology, chemical findings, and physical signs as hypoparathyroidism, but the cause of the disturbance is not due to a lack of parathyroid hormone but to an inability to respond to it.

The syndrome has some developmental abnormalities also which distinguish it from hypoparathyroidism. Patients are short and thick set, have round faces, and brachydactylia with short metacarpals, and metatarsals.

Since then, a few other cases of this rare condition have been described by Jackson et al (1956), Laing (1960), and Hanno and Weiss (1961).

Differential diagnosis is given earlier and consists mainly in the different clinical physical appearance, and the Ellsworth Howard test.

Treatment is not very reliable, but patients may respond to dihydrotachysterol, Albright, Burnett, Smith and Parson (1942).

Oral Manifestations;

Trevathian (1961) described a case of pseudohypoparathyroidism, which was medically examined and diagnosed by Laing (1960). The patient, a boy, aged nearly thirteen years, had abnormal bone formation and calcification, and a history of increasingly severe tetany, since birth, which developed into the typical picture of pseudohypoparathyroidism. Dentally the boy's jaws and mouth were of normal size and shape, and the arches were well formed, with normal occlusion. The incisors were slightly coned shaped but were otherwise normal, and free of surface defects. The other teeth were clinically normal. There was an average caries incidence and slight spacing of the upper anterior teeth. Radiographically the enamel appeared thinner than normal in the upper central incisors. The upper canines, bicuspids, and second molars, and lower second molars and lower left second bicuspids were all present, but unerupted. The upper first premolars and the lower canines had short roots with wide open apical forammina. The apical end

of the developing dentine had a thickened border, ie, it did not finish in the normal knife edge. The main points of interest are the abnormality of the roots which had been formed in the last few years, and the retained deciduous teeth. Medical opinion was that the condition had increased in severity in the past three years. The roots formed and completed before that period, were normal in length and shape. Radiographs taken at the age of thirteen years eight months (nine months after treatment) showed that the roots of the retained deciduous teeth were much more resorbed, and that one of the permanent teeth had recommenced root formation, and that resorption and reshaping of alveolar bone is necessary for normal root formation.

Minrichs (1956) has reported several cases of Idiopathic hypoparathyroidism, and noticed a delay in eruption of the teeth. This case report of Trevathian (1961) supports his findings but is opposed to those of Schour, Chandler and Tweedy (1937) who found that parathormone has no influence on the eruption rate after parathyroidectomy .

PSEUDO-PSEUDOHYPOPARATHYROIDISM.

This very rare disease has the usual anatomical stigmate of pseudohypoparathyroidism present, but serum and calcium levels remain in normal. There is no clinical evidence of hypoparathyroidism and the Ellsworth Howard reaction is normal. Lisser and Escamilla (1962).

The disease has been described by Miles, and Elrick (1955) and Hanno and Weiss (1961).

EXPERIMENTAL HYPOPARATHYROIDISM.

Vassale and Generali in (1900) demonstrated that complete parathyroidectomy caused tetanic convulsions and death; while when one parathyroid was left tetany did not occur.

Loeb (1901) reported experiments on animals in which the induction of muscular twitching occurred by the administration of salts which precipitated calcium and greatly lowered the calcium content of the blood and other tissues.

Sabatini (1901) showed that the nervous excitability of Loeb's animals would be quieted by administrating calcium.

In (1909), MacCallum and Voegtlin demonstrated a 50% decrease in the blood calcium following complete parathyroidectomy.

Keating (1947) describes the changes in dogs parathyroidectomised giving similar findings as in Man.

Effect on the Dental Structures.

Erdheim (1906, 1911) and Toyofuku (1911) published the first fundamental histological studies of changes in rats teeth after parathyroidectomy. The dentine which showed the greatest changes was neither unmineralised or poorly mineralised. There was a zone of incomplete minderalisation consisting of isola ted globules of dentine in an organic framework.

Gies et al (1917) made similar observations, and also Spreter von Kreudenstein (1936).

Erdheim and Albright (1929) made further observations which are alluded to in Albright and Reifenstein (1948), who showed that the acalcification of the dentine of rats teeth following parathyroidectomy ceased when the rat received parathyroid hormone.

Albright and Strock (1933) have observed aplasia or hypoplasia of the teeth when hypoparathyroidism develops before the teeth are fully formed, in their experiments on rats.

Schour, Chandler and Tweedy in (1937) in an interesting article on parathyroidectomised rats teeth showed that for the first twenty postoperative days there is hypermineralisation and this is subsequently followed by a deficiency in mineralisation with irregularly formed dentine which shows occasional vascular

inclusions. Fully formed dentine, show no changes. Disturbances in appositional growth occur only in very severe cases when enamel hypoplasia and vascular inclusions of the dentine are manifest. The eruption of the teeth did not appreciably alter. The cells of the pulp (the odontoblasts) show signs of degeneration and there is the formation of cystic spaces in the pulp.

Muracciole (1957) experimenting on white rats found that parathyroidectomy causes greater changes in the morphogenesis of dental structures than the extirpation of any other gland. Complete decalcification of the dentine and enamel, disorganised formation of the odontoblasts, defects in pulp and malformation of the teeth as they erupt, were all present in the experiments.

Kraintz and Andrews (1961) studies the effect of parathyroidectomy on saliva calcium in the rat, to see if there was a correspondence to the changed serum calcium. While serum calcium levels of the parathyroidectomised animals were reduced to approximately 30% below control level, saliva calcium levels were increased by approximately 30% above the control saliva values. It would seem they concluded that the calcium concentration of pilocarpine-evoked saliva from rats that cannot be used as an index for blood calcium changes produced by parathyroidectomy.

Experimental Parathyroid Replacement Therapy.

The effects of parathormone injections into parathyroidectomised animals (rats) has been studied by Spreter von Kreudenstein (1936) and Schour, Chandler and Tweedy (1937) with the following results; For the first twenty four hours after injection, a layer of well mineralised haemotoxylin staining dentine is deposited against the previously deficiently mineralised dentine. Afterwards when the effect of the parathormone had disappeared on the deficiently mineralised dentine by parathormone, injections given at intervals resulted in a striated dentine as layers of well and poorly mineralised dentine.

The possible close relationship between vitamin D and parathyroid function is suggested by the fact that administration of vitamin D to parathyroidectomised rats is effective in increasing calcification, Schour, Chandler and Tweedy (1937,1949).

The experiments on the parathyroid glands indicate that while calcium can be mobilised from the bones as in hyperparathyroidism, it cannot be withdrawn from the teeth. Stones (1954).

Experimental Nephrectomy.

The kidneys play an important role in the regulation of mineral metabolism.

Tweedy and McNamara (1936), have shown that after nephrectomy in rats the serum calcium remains within normal limits or falls gradually but the serum inorganic phorphorus is increased.

Irving, Weinmann, Schour and Tweedy (1949) have investigated the effect of bilateral nephrectomy on the maxillary incisor teeth, the rats being sacrificed 24 or 48 hours later. The results indicate that there are changes in the dentine which with certain characteristic variations, repeat the pattern of other experiments in mineral metabolism . The dentine disturbances occur in the following order;

1. A narrowing hypermineralised calciotraumatic line staining with haemotoxylin.
2. A Hypermineralised layer which is chiefly eosin staining and corresponds to the preexperimental predentine.
3. A haemotoxylin staining hypermineralised layer, the layer being produced immediately after the start of the experiment.
4. The postexperimental predentine is wider than normal.

In other experiments Irving, Weinmann, Schour and Tweedy (1949) found that massive doses of calciferol injected at the time of operation for nephrectomy did not cause the acceleration of the mineralisation of predentine as in normal animals.

In further experiments, the same authors found that the effect of injecting large doses of parathyroid extract at the time of nephrectomy there was a reduction in the stimulating effect of nephrectomy on dentine formation. In normal animals injection of parathyroid decreases the rate of dentine formation. Irving, Weinmann, Schour and Tweedy, (1949) Stones (1954).

THE THYMUS GLAND.

The role of the thymus in the endocrine system remains an enigma; all attempts to obtain a hormone by extraction have failed. Unexplained are sudden "thymic deaths" from persistently enlarged thymus; likewise the frequent association of thymomas with myasthenia gravis. The clinical picture of Cushing's syndrome in seeming association with carcinoma of the thymus has been convincingly documented in at least five instances. These neoplasms so called "oat cell tumours" show reversion of the normal cell structure of the thymus to an epithelial type; their occurrence with adrenal cortical hyperplasia together with Crooke's cell changes in the Pituitary gland, has been reported. These tumours may elaborate an adrenal cortix - stimulating hormone, accounting for the similarity in clinical findings in thymus tumours and Cushing's syndrome. Whether these thymic tumours are purely incidental or are actually related to the development of Cushing's syndrome (see later) remains uncertain. Lisser and Escamilla (1962).

There have been a good many assumptions as to endocrine functions of the thymus and largely without adequate support. Selye (1949) states that the best established observations concerning the thymus have been brought out during the previous ten years by work concerned with the influence upon this organ of non-specific damage and steroid hormones. It appears that folliculoids and even other steroids to a lesser extent cause rapid thymus involution, not only in intact, but also in adrenalectomised animals. Stones (1954) remarks that the thymus is sometimes hyperplastic in exopthalmic goitre and Addison's Disease.

However, its function remains unknown. Not much more is known of it than is already mentioned, and that it increases in size until puberty and then subsequently atrophies. It consists partly of epithelial cells and partly of small round cells like lymphocytes. Burnet (1963) in a recent article of interest states that the thymus is the primary source of lymphocytes and suggests that the antibody control mechanism is located primary in the thymus.

Therefore its influence on the dental structures is not really known, irrespective of some research done as to this and various observations made.

Thoma and Goldman (1960) refer to a case presented by Ivy (1933) of a woman of 28 years old who had no permanent teeth erupted at the age of sixteen, and who had full dentures made. Radiographic findings revealed a full complement of permanent teeth unerupted. It was associated with dwarfism and an endocrine connection was suggested.

Kranz (1913) described the dentition of a child, aged seven years with out a thymus, who had lost all the deciduous teeth, at the age of four years; and who was edentulous because all the permanent teeth, that were present, according to radiographic examination, had failed to erupt.

Nieddu (1958) gives a description of oral manifestations of thymus dysfunction as follows;

Hypothymism; The hypocalcified maxilla has a tendency to fracture. The teeth are milky white and prone to caries.

Hyperthymism; There is an early eruption of the deciduous and permanent teeth. The teeth are well calcified or may be hypocalcified

No reasons are given for these statements, nor any case reports referred to, to substantiate them.

EXPERIMENTAL THYMECTOMY AND THYMUS ADMINISTRATION.

A good deal of work has been done in this regard in an attempt to detect some indication of the function of the gland. The results have been somewhat conflicting particularly with thymectomy because of the position of the thymus making it difficult to remove completely, and because of ectopic thymus tissue elsewhere, and serious surgical injury to young animals may cause deficiency symptoms which may be attributed to the thymus when it is not the primary cause at all. Hawker (1950).

Klose and Vogt (1910), working independently, demonstrated osseous disturbances and growth retardation following thymus ablation.

Gudernatsch (1914), and Romeis (1914) in tadpoles, observed marked acceleration of growth after the oral administration of calves thymus tissue. Uhlenhuth (1919), could not confirm this report. And in mammals similarly treated, some workers have noticed acceleration while others report retardation of the growth rate, or no effect whatsoever.

Asher (1934) prepared an extract which he called "thymocresin" and which accelerated the growth rate, in rats.

Rowntree et al (1934, 1935) have reported that the continuous administration of an extract prepared by Hanson called "karkinolysin", through successive generations of rats, resulted in marked precocity and an accuring acceleration in the growth and development of the offspring of parents treated for two generations. This precocity was intensified when the successive generations were also continually treated, so that litters of the sixth generation were born with their eyes opened and teeth erupted, events which normally do not occur until the third or fourth, and ninth to tenth days of life respectively. This was associated with sexual precocity. After some months, the growth rate slowed down so giantism did not occur.

Subsequently, Rowntree et al (1938) found that the injection of substances found in thymus extract, namely glutathione, ascorbic acid or cysteine, separately or in combination also exhibited the capacity to accelerate growth or development of the offspring of

treated rats.

Rowntree et al also experimented with thymectomy in rats (1938) but retarded of growth whilst occuring in a progressive way, beginning with the second generation, was not so spectactular as might be expected.

Chiodi (1938) and Segaloff and Nelson (1940) repeated Rowntree's work, but could not confirm it.

Shay et al (1938) found that intense irradiation of the thymus caused stunting of growth in rats.

It has been suggested that an explanation of Rowntree's experiments, is that the changes in growth from the Hanson (and Asher) extracts administered, may be due to a nutritional rather than endocrine phenomena of substances in the extract, Hawker (1950).

Recent experiments of Miller (1961) who removed the thymus glands of unanaesthesised mice at one day old found that the animals lived normally for three to four months, then died for reasons not fully known yet. It has been found that such mice loose most of their capacity to produce antibodies. It is clear that the thymus is the primary source of lymphocytes which play a role in maintaining the integrity of tissue. Burnet (1963).

It would seem that at this stage, that the thymus cannot conclusively be regarded as an endocrine gland, its function remaining as Lisser and Escamilla (1962) state, an enigma.

THE PANCREAS.

INTRODUCTORY.

The pancreas is a dual gland possessing both endocrine and exocrine functions. The endocrine secretion is called insulin and exerts a profound effect on carbohydrate metabolism.

The pancreas is a soft, lobulated, reddish gland lying on the posterior abdominal wall, its right end in the concavity of the duodenum and its left end touching the spleen, its length being 12-15 cms and weight about87 Gm. It develops from a ventral and dorsal outgrowth from the alimentary canal. Cunninghan (1947) . The bulk of the pancreas is composed of exocrine tissue, the endocrine tissue being distributed thoughout the organ, between the exocrine elements in the form of small cell accumulations, called "Islets of Langerhans".

Four types of cells have been described in these Islets, but the alpha cells (acidophilic, and alcohol-insoluble granules present) which are less numerous, and the beta cells (basophilic and alcohol-soluble granules), which are the most numerous, smaller, and generally occupy the periphery of the "islets". These beta cells are the producers of insulin, the function of the alpha cells being not accurately known. Selye (1949), Ham (1954). No other hormones have proved to be found associated with the pancreas, Selye (1949).

The function of Insulin.

Hawker (1950) gives the following threefold function of the hormone on carbohydrate metabolism,

1. Enables the tissues to burn sugar (stimulates tissue oxidation)
2. Increases the ability of the liver and muscles (mainly) to store sugar in the form of glycogen, (stimulates glycogenesis).
3. Inhibits the formation of sugar from amino acids and fat in the liver, (inhibits gluconeogenesis).

A normally functioning liver is also necessary in carbohydrate metabolism as well as insulin. There are many factors involved in a normally functioning liver such as other hormones (pituitary and adrenal) and the autonomic nervous system.

The rate of insulin is probably regulated by the blood glucose level, the vagi herves, indirect (and possibly direct) control of the anterior pituitary gland. Selye (1949), Hawker (1950).

Insulin appears to be an antagonist to the diabetogenic fraction of the anterior pituitary and the adrenal secretions and when deficient there is an inhibition of glycogen storage, with increased blood sugar. Marble (1947).

Normally all revelant factors are balanced to give a consistant blood sugar level of 80-120mg / 100mls. The blood sugar comprises the total reducing bodies in the blood - consisting mainly of glucose, Conybeare and Mann (1952).

There is still a good deal not known as to the physiology of the Islets of Langerhans.