HYPERINSULINISM. (spontaneous hypoglycaemia).

Lisser and Escamilla (1962) classify hyperinsulinism into four groups.

1. Organic hyperinsulinism. Usually caused by a single beta-cell tumour of the Islets of Langerhans, in the form of an adenoma (or multiple adenomas to a much less extent).Carcinoma may also occur.

2. Relative hyperinsulinism. Occurs when insulin antagonistic hormones are deficient (as in impaired function of the anterior pituitary or adrenal cortex or in severe hypothyroidism).

3. Functional hyperinsulinism. Occurs without an anatomical lesion and is the most common form of hyperinsulinism. The condition does not worsten as in the first two types. It is due to alimentary disorders (too rapid absorption of carbohydrate results in release of large amounts of insulin), nervous or reactive disturbance from autonomic imbalance, deficient intake of carbohydrate as starvation hypoglycaemia in nervous anorexia, overdoses of insulin preparations, nontropical sprue, etc.

4. Idiopathic hyperinsulinism. This spontaneous hypoglycaemia occurs in children under two years of age, and there is spontaneous recovery as the child grows older, and it may be familial. The manifestations may be vague and fleeting and are precipitated by hunger, fright, teeth troubles, physical exhaustion, of loss of sleep. Early recognition is important to prevent irreversible brain damage.

Silverman (1961) states that hyperinsulinaemia may be initiated by a stressful dental procedure.

Clinical Features.

Lisser and Escamilla (1962) enumerate the symptoms and signs as follows;

1. Attacks vary from single fatigue to agitation and violent behaviour, disorientation, mania, delirium and coma.
2. Onset accompanied by profuse perspiration.
3. Often numbness around the mouth.
4. Fasting or hunger often precipitate attacks.
5. Rolling or glassy eyes.

Laboratory findings; are also enumerated as follows by Lisser and Escamilla (1962).

1. Low blood sugar level.
2. Glucose tolerance test; a value of 45mg% after five to six hours, or less in the presence of hypoglycaemic symptoms that are relieved by intravenous glucose administration is diagnostic.
3. Intravenous tolbutamide test.
4. Tests for adrenal cortical, pituitary, thyroid deficiences,

Oral Manifestations;

There is often numbness around the mouth present, Lisser and Escamilla (1962), Selye (1949), remarks that the lips are commonly affected.

Lisser and Escamilla (1962) comment that idiopathic hyperinsulinism is sometimes caused by teething troubles in children.

Treatment.

1. Surgical exploration for a pancreatic tumour is mandatory after elimination of other possible causes, and its removal if present.
2. Partial or total pancreatectomy occasionally beneficial in the absence of tumour, or in the case of diffuse adenomata.
3. Diet control, with low carbohydrate, high protein, with frequent feedings is important in the relative, functional and idiopathic types.
4. Endocrine substitution therapy, such as thyroid substance.
5. Acute attacks treated by sugar administration orally or intravenously. Lisser and Escamilla (1962).

Selye (1949) adds that care must be exerted to prevent the patient hurting themselves during convulsive attacks.

Prognosis.

Is usually good when treatment is given following correct diagnosis. Early diagnosis and treatment is desireble to prevent irreversible damage to the control nervous system.

HYPOINSULINISM (Diabetes Mellitus)

Diabetes Mellitus a metabolic clinical syndrome, is generally considered to be due to a deficiency in insulin production, but a wider conception of its aetiology includes any disturbance of the normal balance of regulatory endocrine factors that will result in the symptom complex. In the majority of cases of diabetes mellitus there is an actual deficiency of insulin, Hypoinsulinism and diabetes mellitus are not synonymous terms, in that, while all cases of the former are diabetics, all diabetics do not exhibit hypoinsulinism. Hawker (1950).

Other types of diabetes mellitus are due to pituitary disturbance called hypophyseal diabetes, and due to adreno-cortical disturbance called adrenal diabetes, and should be regarded a s separate distinct disease entities, Selye (1949).

Diabetes mellitus was known to the ancient Greeks and Romans. Celsus in his writings (30 B. C. -50 A.D.) remarked on the polyuria, polydipsia, and emaciation associated with diabetes. The disease has been referred to many times since then.

Cheusel (1807) proved that the sweet taste in diabetic urine was due to glucose. The name diabetes mellitus simply means, a sweet copious flow of urine.

Langerhans (1869) discovered the islets cells, called after him. Minkowski (1889, 1893) stressed that the islets of Langerhans and not the acinar tissue are involved in diabetes.

The word "insulin" was used to designate the internal secretion of the pancreas as early as (1909), but it was not detected until Banting and Best (1921) working in Macleod's laboratory (see Selye, (1949), for graphic description of this interesting research work) suceeded in preparing a clinically useful pancreatic extract. Others working at about the same time also were successful in this field. Insulin was first isolated in crystalline form by Abel (1925)

Aetiology.

Diabetes mellitus is a condition mainly characterised by persistant hyperglycaemia and glycosuria. It is generally assumed that the primary type of diabetes mellitus is due to an insufficiency

of insulin production of the pancreas, which may be due to a primary failure of the islets of Langerhans, (eg. destruction by tumours, inflammations) or to their secondary breakdown resulting from excessive stimulation by antero-pituitary hormones (eg in certain types of anterior lobe tumours and hyperplasias). Selye (1949), Conybeare and Mann (1951).

Selye (1949) classifys the disease as follows:

1. Infantile and juvenile diabetes - which tend to be rapidly progressive and lead to acidosis and cachexia but rarely to gangrene or skin infections. There is a marked somatic growth urge.
2. Adult diabetes, It may, or may not, lead to cachexia and it is frequently accompanied by adiposity.
3. Senile diabetes. The progress of the disease is slow and there mat be even spontaneous regressions. Cachexia is rare, and the cardiovascular manifestations of gangreme and trophic disturbances are more common.

Histopathology.

If morphologic lesions occur in the pancreas, they would be either due to hyalinization of the Islets of Langerhans which is the most common case, or due to hydropic degeneration of the beta cells, or due to round cell infiltration of the Islets of Langerhans and rarely it is due to acute pancreatitis and tumours, Opie, Weichselbaum, Harris, Selye (1949), Muir (1951).

Incidence.

Marble (1947) states that there were at least two million diabetics in U.S.A. in (1947), but Wilkinson and Krall (1947), suggest that there may be even twice that number. Diabetes now ranks eighth place as cause of death in U.S.A.

Narborro of Middlesex Hospital (1962) states that six out of every 1,000 are known diabetics in England, but there would be many more unknown.

Occupational factors (sedentary, well-fed persons in urban areas being more prone to it) and hereditary factors (it is established that diabetes is an inheritable disease) and racial

factors (Jews, Teutonic, etc. more prone to it) all have a distinct bearing in the incidence of the disease. Selye (1949).

Clinical Features.

In its early stages it is not characterised by typical manifestations, but as the disease develops, every tissue of the body becomes affected, Marble (1947). The chief symptoms of uncontrolled diabetics are almost continuous fatigue, polydipsia and polyphagia often, but not always accompanied by a loss of weight. Not infrequently various types due to cardiovascular disturbances are amongst the presenting symptoms. The notoriously low resistance to infection with diabetics is of particular importance, manifesting itself in respiratory infections particularly.

The skeletal system is not specifically affected by diabetes mellitus although if the disease develops during childhood, the growth rate is sometimes greatly inhibited. In the case of so called "pancreatic dwarfism" or "infantilism" the impairment of skeletal development may also be partly due to interference with the external secretion of the pancreas and the resulting impairment of calcium absorption. Quite frequently diabetic children, though underweight, are overgrown during the first few years of their illness. This may be due to excessive anterior pituitary function.

Cardiac disease is perhaps the most common immediate cause of death in diabetics, involving diseases of the coronary arteries, and arteriosclerosis of the vessels leading to angina pectoris. Also generalised arteriosclerosis and gangrene of the extremities are common and serious complications of diabetes. This may also affect the eyes, kidneys and brain. Seagar (1959, 1963) comments on these complications of diabetics in aging persons.

Staphylococcal infections and puritis of the skin and appendages are also common clinical findings. Xanthochromia, which renders the skin yellow, especially the palms of the hand, and the nasolabial folds also occurs but is only a concern cosmetically.

Diminished sexual function sometimes occurs in both men and women diabetics, Selye (1949), also increased foetal mortality if diabetic pregnancy occurs, Marble (1947).

Although the metabolic disturbance in diabetes mellitus primarily involves carbohydrate metabolism the disease, particularly in its severe form, also involves protein and fat metabolism. The abnormal breakdown of fats producing Ketone bodies, when accumulated in the blood produces ketosis and diabetic coma, and they are also excreted in the urine and from the lungs, Conybeare and Mann (1952).

Changes in the Oral Cavity.

Diabetes if uncontrolled, may give rise to serious complications aggravating any concurrent conditions which is due in a general way to lowered resistance to infection in diabetics. Also infections anywhere adversely affects diabetics. However, oral manifestations on the whole are not spectacular nor by any means diagnostic, Thoma and Goldman (1960).

Sheridan et al (1959) comments in his review that the evidence of leading medical authorities seems to indicate that some of the most common symptoms and signs of diabetes mellitus occur in the oral cavity. The most frequently reported are dry or burning mouth, tender gingivae, pain with percussion of the teeth and dry sockets. The two most often discussed radiographic findings in diabetes are alveolar bone loss and widening of the marginal periodontium. Most of the published material, however, must be recognised as being in the realm of opinion rather than fact.

As Shafer, Hine and Levy (1963) point out there are probably no oral lesions found with correctly controlled diabetes.

In the preinsulin era the juvenile diabetic did not survive long enough to manifest mouth changes, and in the protamine zinc insulin era since (1938) the treatment improvement meant a better control of the disease and less changes in the oral cavity to be seen, Pollock et al (1947).

The diabetic patient is subject to the same lesions in the oral cavity as the non-diabetic patient, but they vary in severity in accordance with the degree of the diabetes and the degree of control, Pollack et al (1947)

Massler (1949) examined the oral flora of 288 controlled and uncontrolled diabetics found a high prevalence of staphylococcus

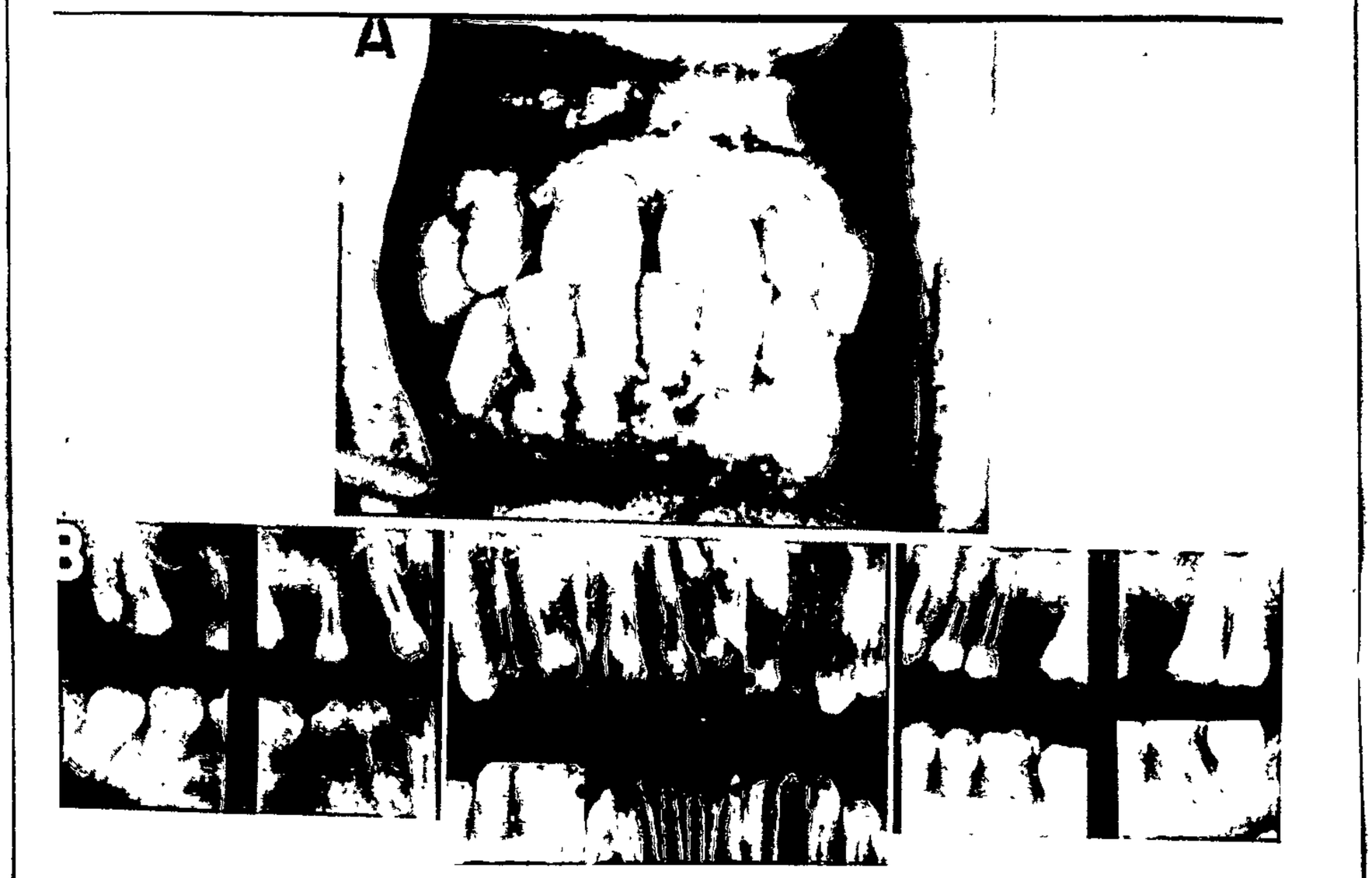

Fig. 22.

Diabetes Mellitus. Patient aged 23 yrs. who had the disease for two years. Teeth were mobile, gingivae receded and oedematous, alveolar bone loss.

Cheraskin and Langley (1956).

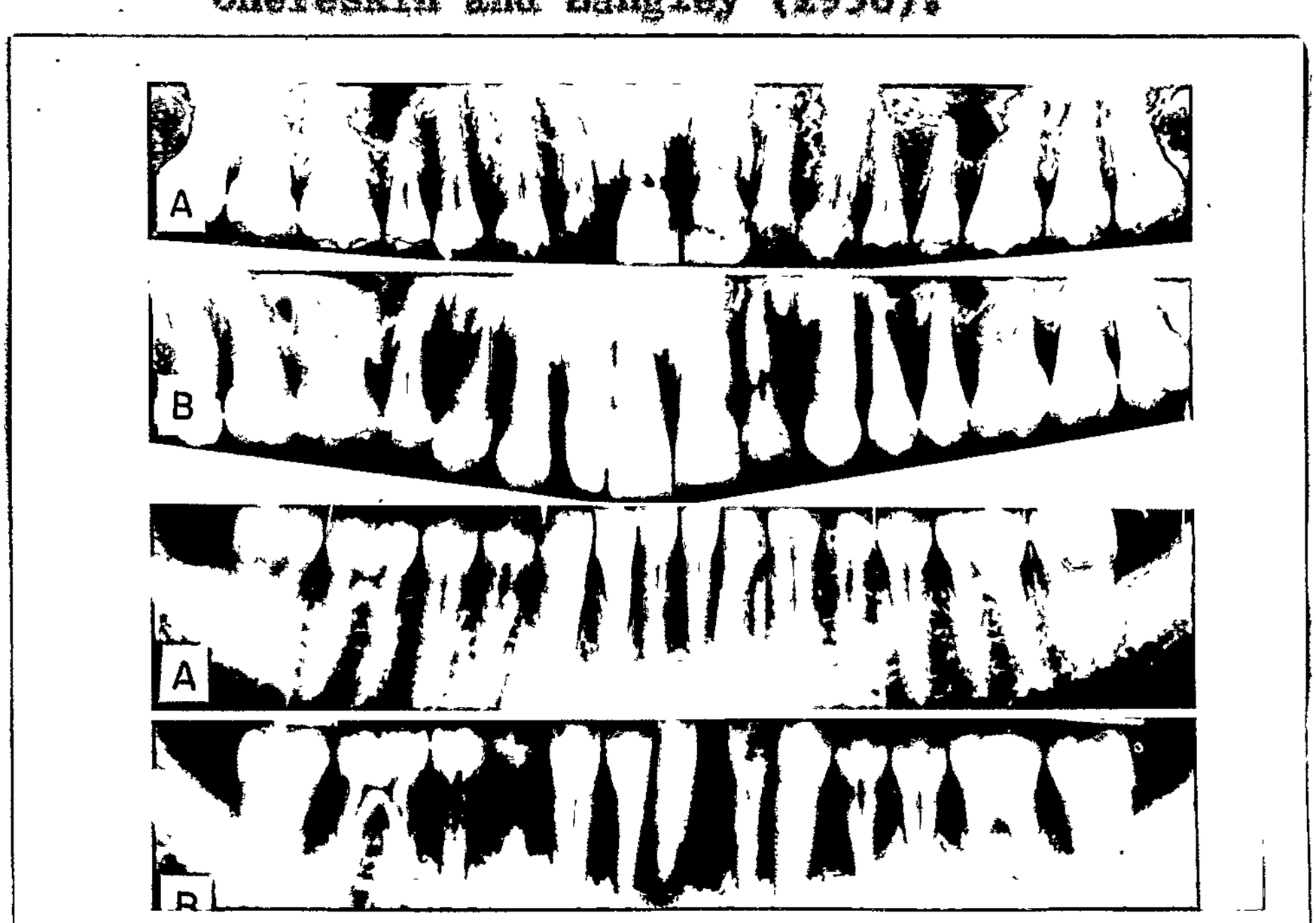

Fig. 23.

Diabetic periodontosis, in man aged 28yrs. with a history of the disease of 6yrs. duration. Three yrs. elapsed between radiographs in A and B during which time the disease was untreated. Shafer, Hine, Levy (1963)

aureus and beta haemolytic streptococci on the pillars and lower anterior gingivae.

The teeth and jaws of controlled diabetic children are normally developed according to Kent (1931), Ziskin and Siegel (1942). However, Rutlidge (1940) reports periodontal disturbances (non specific gingival and marginal, vertical and horizontal atrophy) in 80% of the twenty diabetic children, ages eight to eighteen he examined. And periodontal widening in fourteen out of the twenty. Zilz (1915) who studied 100 diabetics in Veinna found no paradontosis in children aged five to fifteen years.

Sheppard (1936), Hilming (1938), Scheff (1938) report similar findings as Zilz (1915).

In the literature a wide variety of oral manifestations have been reported in adult diabetics including sore teeth, periodontosis, sensitivity to percussion, gingival abscess, loose teeth, alveolar resorption, foul breath, thirst and dryness of the mouth, fissured tongue, stomatitis, gingivitis, hypertrophy of the interdental papillae, gingival bleeding, pocket formation, paradentosis, periodontoclasia, pyorrhoea alveolaris, sensitive cementum, circular caries, thrush, thick gums with violacious colour, periodontal widening and increased cervical depth, by the following authors;

Sieffert (1862), Schmidt (1881), Magitot (1882), Bonieux (1883) Zilz (1915), Citron (1928), Williams (1928), Joslin (1928), Niles (1932) Schonfelder (1932), Rowe (1932), Beardwood (1933), Reynolds (1932), Aiquier (1935), Sheppard (1936), Hutton (1936), Rudy and Cohen (1938), McCulloch and Resch (1941), Lyons (1943), Ziskin et al (1944), Knichknowy et al (1950), Sheridan (1959), etc. Many of these can be dismissed as coincidental findings somewhat affected by the underlying diabetes. The dentist can suspect diabetes by the rapid spread of any oral infection, Pollock et al (1947).

Mohnicker and Ulrich (1957) examined 222 diabetic patients and stated that although there were a small number of them free, or comparatively free, of pathological symptoms in the oral cavity, in patients mainly belonging to the short and stocky type the existance of a relation between diabetes and oral or dental diseases

can be assumed.

Affects on Alveolar Bone.

Sheppard (1936) states that there is a large incidence of unusual alveolar resorption between the ages of fifteen and 40, in diabetic patients, which can hardly be attributed to local causes and which is not found in healthy persons. Niles (1932) even suggested that a routine urine examination should be carried out in all cases of alveolar resorption. Many other writers have linked alveolar bone loss with diabetes such as Zilz (1915), Black (1918), Kent (1933), Rudy and Cohen (1938), Rutlidge (1940), Sheppard (1942), Sindoni (1954), Robinson (1954). In most of these cases the authors did not use non-diabetic controls but relied entirely on clinical observations to establish bone loss. Other reports have been better controlled such as those of Sheridan (1959) who found that loss of alveolar bone occurred in 42 patients that alveolar bone resorption occurred in an increasing manner, according to increasing severity of the diabetes. Lovestedt (1943) examined 509 patients and compared them with 1023 controls and found that periodontal disease was more prevalent in the diabetic patients. Glickman in his study on rats treated with alloxan (producing alloxan diabetes) found less of alveolar bone adjacent to gingival inflammation. Copeland (1955) and others have found bone losses in the feet of diabetic patients where there is an adjacent inflammatory lesion.

Provenza et al (1959) found that persons with periodontal disease had more constricted arterioles in the periodontal membrane. Quintarelli (1957) found that degenerative changes in the mandibular artery and arterioles in cadavers varied directly with the extent of the periodontal disease. Thomas (1946) expressed his impression that vascularity of alveolar bone decreases with age. It is known that arteiosclerosis is a feature of diabetes mellitus as already mentioned and there may be a connection between this and alveolar changes and periodontal disease. Ray (1948) found that there was thickening of blood vessels and endothelial changes in the gingival tissues of people with diabetes. Monnicke (1957) found that in

222 people with diabetes without vascular changes 39% had periodontal changes, whereas in 278 people with diabetes and vascular changes 69.9%, showed symptoms of periodontal disease, However, calculus and many other factors may influence the loss of bone in the alveolus Belting et al (1953) said that the loss of the teeth was important in rightly evaluating alveolar bone losses. Kent (1933) found that in 5,000 patients with diabetes most of them who had lost teeth, lost them as a result of periodontal disease. Lovestedt (1943) observed that patients with diabetes were more frequently edentulous than non-diabetic controls.

Mackenzie and Millard (1963) in a very interesting and detailed article co-related some of these previous findings by comparing three groups of persons one comprising 60 confirmed diabetics, another with 64 suspected diabetics, and 54 arteriosclerotic non-diabetic patients. They concluded that although a relation between arteriosclerosis and diabetes had been demonstrated, a positive influence of arteriosclerosis on alveolar bone loss in diabetes mellitus has not been found. There is a high positive relation between calculus and alveolar bone loss, but there is no significent increase in calculus in diabetic patients. Although a pattern of bone loss by region does exist, diabetes mellitus does not alter this pattern. Diabetes mellitus itself is not associated with increased alveolar bone loss. Their conclusions seem to summarise the stage reached in research on this subject.

Affect on the Teeth.

In the past, several reports have appeared indicating that dental caries experience in diabetics who were controlled differed from other population samples, such as the reports of Ersner (1926) Boyd and Drain (1928), Kent (1933), Rudy and Cohen (1938), Rutlidge (1940), Boyd (1943). More recent reports however, using more refined methods of determination tend to invalidate these reports and several of the authors have revised their opinions. It would appear that to-day, the generally accepted belief is that diabetics do not suffer significantly from any other individuals as regards caries experience, Boyd (1944), Polleck et al (1947), Cohen (1947) Joslin et al (1952).

Periodontal changes.

This has been reported more than anything else in association with diabetes mellitus, ranging from hypertrophy of the gingivae, and mild gingivitis down to severe alveolar bone loss (see "Affect on alveolar bone").

Various terms have been introduced in the literature to describe these changes such as diabetic stomatitis, diabetic periodontal disease, diabetic gingivitis, diabetic periodontplasia.

It presents itself as similar to that found in non-diabetics except that there is an earlier appearance and a more rapid progress of it in diabetics, Pollock et al (1947). However, they state that it is probably only an extension of the existing marginal gingivitis.

Hirschfield (1934) reported in detail as to oral manifestations of diabetes and believes that there are definite periodontal symptoms of acute periodontal abscess and pedunculated proliferative gingival margins. The most comprehensive report was that of Kent (1933) who studied 5000 diabetics, and divided them into three groups, of those under twenty years, twenty to 50 years and over 50 years. Those in the 20-50 age group, exhibited the greatest oral changes involving pocket formation.

Ziskin et al (1944) studied sections of gingival tissue from insulin and diet controlled diabetics and found hyperkeratinisation, hyperplasia of the epithelium and of the connective tissue, decreased glycogen deposition. Increase in fibroblasts and prominence of the capillary bed with reduction if inflammatory exudate in the corium. They state that the underlying factors in producing the gingival changes in diabetics may be the nutritional and metabolic imbalances which the diet or insulin treatment only partly corrects.

Glickman (1946) experimented with alloxan diabetic rat and found no periodontal changes, but that 39% had alveolar bone changes.

Mallaowalla and Koppikar (1958) summed up their investigation of human diabetics by saying that in controlled diabetics, there are no characteristic gingival or periodontal lesions. This was further supported by the survey of Baird (1960) who used a special dental score method of dental examination.

Hirschfield (1934), Rutlidge (1940), Comroe et al (1954), all state that a chronic gingivitis is always present.

Pollock (1947) states that the periodontitis occurring in the uncontrolled diabetic may be due to the negative nitrogen balance with the subsequent drain on the body proteins. Since calcium metabolism depends on protein metabolism, this may be a causitive factor in the alveolar bone resorption. A second point advanced is that a decreased resistance to infection may be due to a decreased number of gamma globulin immune bodies, which are a function of the protein metabolism, and which in starvation and diabetes disappear from the blood.

Glickman (1958), concludes after accessing available information, that periodontal disease in diabetics presents no unique microscopic factors which warrant a diagnostic specific disease entity. It has not been demonstrated that diabetes is responsible for onset of gingival disease, or for the production of specific gingival changes.

Shafer, Hine and Levy (1963) comment that patients with untreated or inadequently controlled diabetic mellitus, exhibit a fulminating periodontitis with periodontal abscess formation and inflammed painful, and even haemorrhagic gingival papillae.

Swenson (1963) reports a case of an uncontrolled diabetic woman, 23 years old, in which rapid deteriorating of the periodontium with periodontal disease and severe alveolar bone loss and pocket formation over a period of 35 months occurred, being attributed to the uncontrolled diabetes.

Periodontal Widening was observed in the findings of Rutlidge (1940) in fourteen out of twenty juvenile diabetic patients. The observations of Rudy and Cohen (1933) in that respect are in agreement with those of Rutlidge. However Ziskin et al (1944) could not demonstrate periodontal widening in this series of cases. Sheridan et al (1959) report that in patients with decreased glucose-tolerance patterns (diabetics) there was a 62% evidence in periodontal widening. These investigations also observed that the occurrence of these findings, decreased with an increase in sugar tolerance. The findings of Manson-Hing and Chereskin's

(1960) suggest that the two radiographic signs - alveolar bone loss and periodontal widening are associated with hyperglycaemia, and hypoglycaemia, and that the findings run parallel to those of increasing age.

Other Oral Changes.

Brand (1850) quoted by Rutlidge (1940) first described the diabetics breath, as having a "fruity odour". It has also been described as resembling "new hay" or "decaying apples" or acetone.

Calculus deposits have been described as common in diabetics, Kent (1933), Rudy and Cohen (1938) and others due to the acidosis and the large calcium output of the saliva by Rutlidge (1940), but Mackenzie and Millard (1963) found no greater incidence of calculus in diabetics.

Glossodynia and Xerostomia is said to occur in many cases, and is said to be due to the fluid loss, Thoma and Goldman (1960), Shafer, Hine and Levy, (1963). Comroe, Collins and Crane (1954) describe the diabetic tongue as enlarged, thick, raw, fissured, and ham coloured. Sheridan et al (1959) found that these findings as to the tongue occurred more often in patients with decreased glucose tolerance.

Strean (1938) referred to puritis gingivae as occurring sometimes in diabetics and reported several cases of it.

Hirschfield (1934) has reported simple or multiple gingival abscesses associated with diabetis stomatitis.

Comroe, Collins and Crane (1954), and Sheridan et al (1959) report several other oral symptoms associated with diabetes, occasionally found, such as cervical sensitivity, and the frequent occurrence of dry sockets.

Vaccari (1938) examined the mouths of 100 diabetic patients, and amongst other things, found that there was a sweetish taste in the mouth, in 5% of cases.

Laboratory Findings.

In frank diabetes there is;

1. Hyperglycaemia and Glycosuria. Blood sugar is elevated to

120mg% or more after eight to fourteen hours of fasting. A glucose tolerance test is best employed to make an accurate determination of the hyperglycaemia.

2. Hyperlipaemia, is also a common occurrence in diabetes, so much so that the plasma may assume a milky appearance. Hypercholesterolaemia is an approximate index of the lipaemia in general, and to some extent of the severity of the diabetes.

3. Ketosis occurs in severe cases, with excessive quantities of ketone bodies in the blood. Varying degrees of ketonaemia occur, and is determined by ketonuria tests. Ketonuria is closely related to the degree of diabetic acidosis, and indicates a prompt institution for therapy. Acetone is the first of the ketone bodies discernible in the urine. Selye (1949),

Differential Diagnosis.

1. Renal diabetes. Glucose appears in the urine but the blood sugar remains normal or subnormal.

2. Alimentary glycosuria; is always due to a lowered renal threshold for glucose. Prolonged starvation and liver cirrhosis may also cause glycosuria.

3. Intracranial pressure due to tumours may cause glycosuria and hyperglycaemia.

4. Nephrosis may cause decrease in renal threshold for sugar, but is also accompanied by other manifestations of hephrosis.

5. Metabolic disturbances causes other sugars to appear in the urine; and pregnancy and lactation, with lactosuria may also be confused with diabetes.

6. Hyperthyroidism is frequently associated with decreased renal threshold for glucose, but may be associated with true diabetes mellitus.

7. Various types of hyperpituitarism, especially acromegaly and Cushing's Disease, are often accompanied by glycosuria and hyperglycaemia. The same is true of the various hyperplasias and tumours of the adrenal cortex, which lead to an increased production of glucocorticoids. Other endocrine manifestations of these syndromes assist in the differential diagnosis.

8. Hypoglycaemia, glycosuria, ketosis or acidosis. Selye (1949) Muir, (1951).

Treatment.

1. Dietary control. In mild diabetics, this is all that is necessary to maintain the correct balance. Reduction in carbohydrates expecially, and rigid calorie control, are the chief considerations.
2. Insulin therapy, which is balanced with the diet;
3. In diabetic coma, immediate insulin therapy intravenously must be given. Selye (1949) Conybeare and Mann (1952).

The trend today, as suggusted by Narborro of Middlesex Hospital (1963) and Seagar (1963), is toward dietary control, whenever possible without insulin.

Prognosis.

This depends on the length of time enlarged between the onset of the disease, and commencement of treatment, and also on the intelligence and co-operation of the patient.

If the condition is kept controlled, life expectancy is almost as great as in non-diabetics, according to statistics. Selye (1949).

Dental Treatment of Diabetic Patients.

In order to treat the oral manifestations of diabetes mellitus, as with any systemic conditions with oral manifestations, the underlying cause must first be considered. No periodontal treatment or any surgery should be performed on diabetic patients, without bringing the patient under control, Thoma and Robinson (1955), Thoma and Goldman (1960), Archer (1961), Thoma (1963), comments that uncontrolled diabetes is a contraindication to oral surgery, because of the predisposition in diabetics to wound infection with an extention into the surrounding tissue. This is due, he states, to;
1. Peripherial circulation is reduced somewhat owing to cholesterol deposits in the vessels (premature arteriosclerosis).
2. The high percentage of sugar in the body fluids helps bacterial growth.

Consultation with the patient's physican is advisable before

undergoing dental surgery, Shafer, Hine and Levy (1963), and also during pre-operative, and operative and post-operative periods, Silverman (1961).

Bausouin et al (1938) pointed out that diabetics are poor risks for general anaesthesia, and recommended intravenous injection of insulin be available in case of emergency operations. Silverman (1961) advises that a sugar solution be kept available also. He advised that the insulin be cut down to compensate for the reduced food intake during post-operative period, which is a problem with diabetics undergoing surgery.

There is considerable difference of opinion whether local anaesthetic solutions containing adrenaline (epiniphrine) should be used on diabetic patients. The blood sugar level while the patient sits in the waiting room prior to the extraction of a tooth, has been examined by Chereskin et al (1960) who state that it is not appreciably altered unless the patient is very apprehensive due to a previous bad dental experience. So adrenaline should not cause any adverse effects normally, Silverman (1961) states that local anaesthesia, rather than general anaesthesia, is the choice for diabetes. The patient should be told to examine his urine after any procedure involving anaesthesia.

Diabetes Mellitus. (insulin deficiency) is one of the most widely recognised diseases in which there is significent, clinically evident retardation in the repair of wounds after surgical operations such as tooth extractions, such wounds are notoriously slow in healing and often show complications in the repair process. The exact mechanism of this, is not known but is probably related to the disturbance in carbohydrate metabolism at the cellular level in the local area of the wound. Shafer, Hine and Levy (1963).

Sindoni (1958) advised that it is best to consult the patient's physician rather than take the patient's word, that his diabetes is under control.

Östrander (1958) also advises that it is best to consult the dental patient's physician before doing any dental surgery. He also suggests giving pre-operative sedation to minimise stress

reactions and the increase in blood sugar associated with it.

Antibiotics as a prophylactic measure are unnecessary unless the diabetic is uncontrolled, when it is advisable to prevent infection developing, following dental surgery. Silverman (1961) Archer, (1961), However, Thoma (1963) recommends the use of prophylactic antibiotics.

Silverman (1961) comments that the two hazzards of the treatment of diabetics surgically are poor healing, and the possibility of infection, but both can be adequately controlled with proper techniques.

The diabetic dental patient should be instructed as to the importance of scrupulous home dental care, and prophylaxis to avoid spread of infection, Silverman (1961).

EXPERIMENTAL DIABETES.

Oral Manifestations of Experimental Diabetes.

Extensive experimental work has been carried out in a general way on diabetes mellitus and is largely recorded by Bell (1948).

The first experiments on animals were on pancreatectomised dogs, and was initially done by Von Mering and Minkowski in (1889), who demonstrated a resultant disease similar in all respects to human diabetes. The relationship of diabetes to the pancreas was thus established.

In recent years, it was found that in experimental animals, the drug, alloxan (ureide of mesoxalic acid), produced a disease somewhat similar to human diabetes, Bailey (1943), Dunn and McLetchie (1943), Gomori and Goldner (1943), Hughs, Ware and Young (1944). In dogs, rabbits, and rats there was found to be a specific necrosis of the Islets of Langerhans in the pancreas, which resembles human diabetes in that both are characterised by hyperglycaemia, glycosuria, insulin deficiency, and hyperlipaemia in severe cases.

The periodontal structures of alloxan treated rats were studied by Glickman (1946), who found the following;

1. No gross pathological findings noted in either the diabetic or the control groups. The similarity of the periodontal structures in both groups was very striking.
2. 39% of the diabetic animals presented pathologic changes in the alveolar bone, with comparable changes in other skeletal bones. This varied in the individual animals and was not co-related to the degree of hyperglycaemia or pancreatic disturbance. It was found that a tendency towards varying degrees of non-specific osteoporosis of alveolar bone unrelated to gingival changes is a feature in individual cases of diabetes mellitus.

Betzler and Riedel (1960, 1961) studied the changes in the metabolism of calcium and phosphorus in the facial bones and teeth of rats with alloxan diabetes, and found the following;

1. Five days after the injection of the alloxan the presence of

symptoms resembling those of periodontitis associated with diabetes mellitus in man. There were no such changes in the control group.
2. Additional studies were made to establish whether alloxan diabetes (and therefore diabetes mellitus) affects calcium and phosphorus metabolism in teeth and facial bones which are reported by Franke, (1950), and Macleod (1951), in diabetic patients. Using radiographic calcium and phosphorus on pregnant albino diabetic rats offspring they concluded from their results that there was no evidence for the assumed relationship between any form of diabetes and calcium and phosphorus metabolic disturbances, with the dental and osseous structures. If this metabolic phenomenom is observed, in dental patients they state it is probably a coincidence.

Since alloxan diabetes is a metabolic disorder that has distinct and numerous differences to human diabetes mellitus the necessity for new methods of experiments became obvious.

An entirely new approach in diabetes research was made possible by Yerganian et al (1957, 1958, 1959, 1961) and Meier and Yerganian (1959, 1961) who developed a strain of Chinese hamster (cricetulus griseus) with spontaneous hereditary diabetes mellitus. Polyuria and polydipsia are the two most prominent clinical signs, and hyperglycaemia and ketosis are additional clinical features.
The pancreatic pathology consists of a beta cell degranulation and hydropic degeneration of the islet cells. The chinese hamster is an excellent animal for dental research. The three molar teeth are in good alignment for histologic sectioning. Both the periodontal and pulpal tissues are susceptible to inflammation while the alveolar bone and connective tissues appear extremely sensitive to systemic disturbances.

Cohen, Shklar and Yerganian (1961, 1963) investigated these pulpal and periodontal changes in twelve Chinese hamsters with hereditary diabetes mellitus using another twelve as controls. Their findings were;
1. Severe periodontal disease in the diabetic hamsters, involving calculus-like deposits on the teeth, migration of the epithelial attachment, with splitting of the attachment and pocket formation

alveolar resorption and excessive inflammatory infiltration. There were all degrees, from mild to severe changes in the hamsters.

2. Pulpal changes were also substantial comprising atrophy of the pulp in non-carious teeth. The nuclei of the odontoblasts and pulpal fibroblasts were rounded and pyknotic, and the cellular membranes were absent. The odontoblast layer was no longer well defined. The dentine showed globular areas. These changes were seen particularly in the molars, but also to a less extent in incisors

3. Carious involvment was much more apparant in the diabetic, than the control hamster. They however, state that no define statement can be made as to this yet, on such a small relative number of animals, and that further investigations are in progress.

These experimental results are very interesting, and in the main, correspond to what is found in the human diabetic patient. The further research on diabetic hamsters should throw more light still on the oral manifestations of diabetes mellitus.

THE ADRENAL GLANDS.
(Suprarenal glands)

INTRODUCTORY

The adrenal glands (or suprarenal glands) were first discovered by Eustachius (1563), who named them "glandulae renibus incubentes". Riolanus (1627) named them "capsulae suprarenales" and Spigelius (1627) used the designation "capsulae renales".

Some clue as to the function of the glands was not found till 300 years after they were discovered, when Thomas Addison (1849) gave a brief description of the disease and the sympathetic nervous system are closely related, was first mentioned by Leydig (1851) and Koelliker (1854). They demonstrated the antatomical difference between the two portions of the gland, the cortex and medulla.

A hormonal function of the glands was attributed to the adrenals by Vulpiosi (1856), and by Arnold (1866), and its physiology was described by Oliver and Schaefer (1894). Takamine and Aldrich (1901), are credited with the isolation of adrenaline, the medullary hormone; and Stewart and Rogoff, Hartman, Swingle and Pfiffner (1927-1930) first isolated the cortical secretions. Much research has occurred since, and many steriod hormones of the cortex have been isolated, and discovered in the urine. Experiments in (1946) evince a close relationship between production and activity of certain cortical hormones and pantothenic and ascorbic acids.

In (1950) the Nobel Prize was awarded to Hench and Kendell, of the Mayo Clinic, and Reichstein and Zurick, for their work on the synthesis and clinical application of cortisone, and of the important cortical hormones.

Normally, there are two adrenal glands comprised of an outer cortex (of mesodernal origon containing three layers of cells), and an inner medulla of epithelial origon comprising about one tenth of the whole gland. The size of the glands average 4cmx 3cm x 1cm. and weigh 10 gm. The medulla is a highly vascular, centralised mass of chromaffin tissue of a dark red colour. The cortex is a thick parenchymatous substance enveloped in a fibrous capsule,

Cunningham, (1947).

The chromaffin system comprises of a large number of masses of tissue similar to the adrenal medulla. It is called chromaffin (or chromaphil) because of its affinity for chromium salts, which gives a brownish reaction. All these masses are in intimate relation to the sympathetic nervous system. The chromaffin system also includes paraganglia associated with the sympathetic trunk, colatteral ganglia of the abdominal region, the two aortic bodies, and possibly the carotid bodies, and glomus coccygeum. There is not such a system with the cortical portion of the gland, although cortical bodies are found at times. Cunningham (1947).

The hormones of the Adrenal Cortex and their function.

The adrenal cortex is indispensible to life. Death usually ensues eight to ten days after complete adrenocorticoectomy.

At least 20 crystalline compounds have been isolated so far, all of which are steroids with the cyclopentanoperhydrophenanthrine ring. It is remarkable that these hormones, with this same nucleus, have such diverse effects, Ham (1953). However, many of these steroids do not appear to have any physiological effects.

The generally accepted classification of the adrenal cortex hormones currently is as mentioned in Wheeler and Jack's "Handbook of Medicine" (1963).

1. The gluco-corticoids, which controls gluconeogenesis from protein, and the deposition of glycogen in the liver-thus is antagonistic to insulin. They also reduce the circulating eosinophils in the blood; and have an anti-inflammatory action when injected, The principle steroids are hydrocortisone and cortisone both of which have an effect on electrolyte balance, and also on the kidney's ability to handle a "water-load" efficiently.
2. The mineralo - corticoids of which the main one is aldosterone ("Electrocortin"); they maintain electroyte balance (causing sodium retention and potassium and calcium excretion) but apparently cannot restore the ability to deal with a "water-load". (desoxycort-one acetate -DCA or DOCA) is a synthetic substitute which fairly effectively takes the place of aldosterone if the latter is not

available though its potency is much less.)

3. Sex steroids, including both androgens and oestrogens. These are closely related to the hormones of the gonads. Their part in sexual differentiation and development is not fully known, but they exert a tremendous influence in adreno-cortical hyperplasia, tumours or overactivity. They are produced in the adrenal cortex but apparently only in small quantities normally, Hawker (1950), Cope (1961).

Cortisone was first synthesied in (1946), hydrocortisone in (1950), and aldosterone was discovered in (1952). Hydrocortisone has an hydroxyl group attached to the carbon seventeen of the cyclopentanoperhydrophenanthine ring; cortisone has an oxygen attached to carbon eleven instead of the hydroxyl group; aldosterone has an aldehyde grouping on the eighteen carbon and no hydroxyl on carbon seventeen. It is probable that cortisone itself is relatively inactive and has first to be converted to hydrocortisone before it can exert its pharmacological effects. It has not been detected in the body although it is present in the urine. Cope (1951).

The adrenal cortex secretes a number of so called 17-ketosteroids (a ketone, i.e. O, group attached to the carbon seventeen), and these can be found in the urine of the normal individual, together with 17-ketogenic steroids the two classes making up the total adrenocortical metabolism. Wheeler and Jack (1963). The androgens are excreted in the urine as 17-ketosteroids but do not appear till puberty, and are responsible for the development of the pubic and axillary hair in women (testosterine plays an additional part in men). These 17-ketosteroids are increased in the adrenogenital syndrome and reduced Addison's Disease. These hormones also cause nitrogen retention and are responsible for protein anabolism for the building up of protoplasm. Conybeare and Mann (1952).

In addition to these active steroids, the following sterols and vitamins have been isolated from the adrenal cortex;

1. Sterols; Cholesterol (a compound of great metabolic importance and is probably the parent substance of cholic acids of the bile,

of Vitamin D_3, and of the steroids of the adrenal cortex, and gonads,) stigmasterol, and ergosterol.
2. Vitamins; vitamins D_3, and D_2, dehydrotachysterol, vitamin C . (vitamin D_2, and dehydrotachysterol are irradiation products of ergosterol) Hawker (1950).

Under ordinary conditions hydrocortisone, and probably also some corticosterone are steadily produced in the adrenal cortex. Until recently, the amount of hydrocortisone produced each day was a matter of considerable conjecture. Recently, however, the introduction of isotope-labelled hormones has made possible the much more direct estimation of production rates. In quiescent males, the production varies from 5 to 25mg daily (with a mean of about thirteen) and the hormone pours via the adrenal veins, into the blood stream, and the concentration varies throughout the day being lowest during the night. During the day it varies between 5 and 25 micrograms / 100mls, with a mean of about sixteen. This is about 1/5,000 of the concentration of glucose in the blood. The hormone is promptly destroyed by the liver, and possibly also in the tissues. Cope (1961).

The formation and liberation of adrenal cortical steroids seems to be dependant on the action of adrenocorticotrophic hormone (ACTH) of the anterior pituitary and a rise in cortical steroid levels in the blood causes ACTH production to cease. Many things, such as pregnancy, stress, trauma, exercise, infection, etc. raises the level of adrenal cortical steroids in the blood. Cope (1961). Wheeler and Jack (1963) adds that aldosteroid is not under ACTH control, ACTH mainly affecting the gluco-corticoids.

Only in the past 25 years, has it been recognised that the adrenal cortex, as such, plays an essential role in maintaining life. Extensive studies of the hormone has occurred during that time, and much has been learnt as to their function, but there is still much not known. When the final story is written, we shall probably find that most of the metabolic interrelationships in human physiology are mediated through the adrenal glands, Shafer, Hine and Levy (1963).

Hormone of the Adrenal Medulla. (adrenaline).

The chromaffin reaction of the chromaffin system is not due to a deposition of chromium but to the oxidation of adrenaline. Adrenaline (epiniphrin) is the hormone of the adrenal medulla and other parts of the chromaffin system. It is strikingly similar in its effects to sympathetic nerve stimulation, and it has been assumed that the hormone acts through sympathetic nerve endings. However, it has a vasoconstrictor action, controls glucose metabolism stimulates the heart, and has other effects which indicate that the hormone does not necessarily act through the intermediary of the nerves without implying that it cannot influence the nervous system. Selye (1949).

The stress reactions of adrenaline referred to by Selye (1949, 1956), are of peculiar interest. There is apparent connection in this, between the production of adrenaline in stress conditions, and the secretion of ACTH, which in turn affects the adrenal cortex.

There seems therefore to be a close connection physiologically between the adrenal cortex, adrenal medulla, anterior pituitary, and also between the cortex and pancreas (antagonists), the medulla and cortex and the thyroid gland, and possibly between the adrenal and parathyroids. Hawker (1950).

The effects of adrenaline and nor-adrenaline (probably a precursor of adrenaline) on the circulating system have been extensively studied. Adrenaline in physiologic doses (1 microgram per kilogram), causes a constriction of the arterioles and capillaries of the skin, mucous and heart muscle. The net results is a rise in blood pressure. It also relaxes the smoothe muscles of the stomach, intestine, bronchioles, wall of the gall bladder, ureter and sphincters of the intestines. Recent studies have shown that under controlled conditions, adrenaline acts as an over-all vasodilator drug and a powerful cardiac stimulant, while nor-adrenaline, in comparible doses, acts as on overall vasoconstrictor.

HYPERADRENOCORTICISM.

Hyperactivity of the adrenal cortex, may produce several different clinical pictures, due to distinctly different, adrenocortical steroids. They are; Cushings Syndrome, adrenogenital syndrome of eitherandrogenic and oestrogenic types or mixed, pseudohermaphroditism of congenital origon, and hyperaldosteronism. Lisser and Escamilla (1962).

CUSHINGS DISEASE AND CUSHINGS SYNDROME.

This rare condition may be mediated either through an increased output of ACTH, (where it is generally called Cushing's Disease), or through an increased adrenal cortical output directly due to tumour formation, (where it is usually called Cushing's Syndrome). It is characterised by a disturbed electrolyte, carbohydrate, fat and protein metabolism. Selye (1949), Lisser and Escamilla (1962).

Originally adenoma of the anterior pituitary resulted in the postulation that there is an increased production of ACTH. However, Lisser and Escamilla (1962)., comment that excessive amounts of ACTH have never been demonstrated. They also state that as a rule, hyaline bodies are found in the basophilic cells of the anterior pituitary, called "Crooke's Changes", which however, may be the result rather than the cause of the disease, as they are also found following prolonged doses of cortisone, hydrocortisone or ACTH, and in association with adrenocortical tumours.

Adrenal neoplasm was found to be the cause in seventeen out of 46 cases, (five malignant), in one series from (1935 to 1955). In children under fourteen years, the literature up to (1956) revealed 29 cases (20 in girls, nine in boys), due to adrenal cortical carcinoma. Pituitary tumours (small basophil) chromophobe adenoma, or malignant tumour) play an uncertain role in pathogenesis. Adrenalectomy in such cases, seems more likely to cause growth, than recession of the tumour, Lisser and Escamilla (1962).

Peterson (1962, 1963) remarks that the ratio of women to men, incurring the syndrome, is about, ten to one. In women, it frequently

has been noted to follow pregnancy. Peak incidence is in the third and fourth decades.

Symptoms and Signs.

As listed by Lisser and Escamilla (1962) they are as follows;

1. Obesity ("Buffalo type", particularly because of hump at back of neck, round plethoric "moonface" appearance, and sometimes exopthalmos also occurs.
2. Weakness and easy fatigability.
3. Skin changes, easily bruised, acne, seborrhoea, and the development of purple striae particularly on the abdomen and thighs.
4. Heterosexual hypertrichosis in women (occurred in 94 our of 97 women in one series) but not as luxuriant as in adrenogenital syndrome. (hirsutism).
5. Diminished sexual function; amenorrhoea, loss of libido, testicular atrophy.
6. Psychic changes are frequent;
7. Headaches, and palpation, and hypertension.
8. Polydipsia, and polyuria when diabetes exists.
9. Occasional deepening of the voice in women.
10. Osteoporosis, manifesting itself occasionally in nontraumatic rib or vertebral fractures;
11. Occasional renal colic from nephrolithiasis.
12. Hypertrophy of the clitoris particularly in cases caused by cortisone, hydrocortisone or ACTH.

Albright and Reifenstein (1948), comment that osteoporosis is a very important clinical feature, of the disease due to lack of formation of bone by osteoblasts.

Laboratory findings;

1. Increased urinary excretion of corticoids (ie 17 hydroxycorticoids Porter-Silber chromogens) over 10mg/24 hours in females and 14mg in males. 17 ketogenic steroids, over 17mg in females and 25mg in males. ACTH stimulates higher excretion level up to five times as much. Excretion levels can be surpressed by dexamethasone, when values fall to about half the basal level in

normals and patients with hyperplasia, but not in those with adenoma or carcinoma.

2. Glucose tolerance tests demonstrate diabetic tendency or actual diabetes mellitus.

3. Blood count reveals polycythaemia (excess of red cells) and elevated haemoglobin is characteristic. Anaemia may indicate an adrenal malignant tumour.

4. Eosinophil count is usually low, and lymphocytes are also usually low.

5. Urinalysis may show glycosuria and also the effects of hypertensive disease (fixed specific gravity, albumin, casts), Lisser and Escamilla (1962).

6. Radiographic findings.

The osteoporosis of the long bones shows up as an increased radiolucency. Collapse of vertebrae and of rib fractures occasionally found. The sella turcica is rarely enlarged. Changes in the laws and lamina dura also occur. Howland et al (1958), Iannaceoni et al (1960), and Lisser and Escamilla (1962) etc.

Levi and Weinberg (1950) reports the occurrence of osteoporosis in 64% of all females and 75% of all males in 51 cases.

Cranio-facial features.

The typical moon faced appearance of patient with this disease, due to obesity is to be noted. Hirsutism of the face in women and exopthalmos, are also significent features. Lisser and Escamilla (1962).

Bone changes in the oral region, in Hypercortisonism.

These relate to the bone changes that occur due to demineralisation (osteoporosis). Selye (1949) and Lisser and Escamilla (1962) state that it affects the skull as well as the vertebrae etc. Selye actually states that it is one of the characteristic features of Cushing's Syndrome. It is also a not uncommon occurrence as a side effect of a prolonged cortisone therapy, causing hypercortisonism. Zegarelli (1959), Stafne and Lovestedt

(1960), and Chatwin (1962), report case, with osteoporosis in the jaws.

Greep (1956) remarks that severe osteoporosis and spontaneous fractures are caused by an overabundence of adrenal hormones in the body, whether produced by disease or by hormone therapy.

Shafer, Hine and Levy (1963) comment that in children with Cushing's Syndrome there may be osteoporosis and premature cessation of epiphyseal growth, while in adults there is severe osteoporosis. Stafne (1952) states that the incidence of osteoporosis of the jaws is not known.

The mechanism of the bone changes is not well understood. Apparently 11-desoxycorticosterone is relatively unimportant in the pathogenesis of the disease, is based on the S-F-N (sugar, fat, nitrogen) hormone group of steroids in which the "N" hormone is considered an anabolic one, stimulating osteogenesis and causing closure of the epiphysis, and the "S" hormone is considered on antianabolic one. The mechanism of osteoporosis is then explained on the basis of an excess of "S" hormone leading to a retardation of osteoblastic activity and a reduction of matrix formation.

It seems that there is a complex interrelationship concerned in the normal and abnormal control of bone growth and maturation, and a good deal of research is being undergone to determine the precise metabolic or endocrine pathways by which particular hormones influence skeletal growth. There has been considerable work on the effects of cortisone on experimental animals. Follis (1951), has shown that cortisone injections in rats produced retardation and arrest of and interference with resorption of bone. In other species, only retardation of bone growth was found.

Frazer and Fainstat (1951) have demonstrated that in certain strains of mice, the injection of cortisone into pregnant females produces a high proportion of cleft palates in the offspring. This effect was not due primarily to the inhibition of growth, since cleft palate was produced even when the cortisone was administered after the palate was already closed. Doeg and Coltman (1956) have recently reported several cases of cleft palate in children born of mothers who conceived while receiving injections of cortisone

or who received injections of cortisone during the first three months of pregnancy. Isaacson and Chaudhry (1961) injected inbred mice with cortisone and observed its teratogenic action on the embryonic palate formation and found results consistant with previous studies. The largest incidence of cleft palates was in the group with the largest dosage of cortisone (100%), and it reduced to a 32% incidence in the group with a very small dosage injected. No changes appeared in the controls.

Anderson (1958) states that cortisone affects the metabolism of bone at three sites; the bone itself, the gastrointestinal tract, and the renal tubules. The changes in bone which ensue are attributed to decreased formation of osteoid tissue, the proteinaceous matrix. Under certain circumstances, the corticosteroids inhibit the absorption of calcium from the intestinal tract, and this is evidenced by an increased faecal excretion of calcium. It has also been found that administration of cortisone may increase the urinary excretion of phosphorus by depressing reabsorption of phosphate by the renal tubules. Cope (1961) states that the steroids provoke a negative balance of calcium largely owing to increased faecal excretion.

The histologic aspect of bone changes in hypercortisonism are different from these which are seen in hyperparathyroidism in that there are no cystic changes or giant cell formations. The bone spicules are reduced in number and thickness, which gives the decreased density appearance on the radiographs, Stafne and Lovestedt (1960).

The radiographic appearance of the jaws in hypercortisonism (including Cushing's Syndrome) is fine and indistinct trabeculae, thinning or obliteration of the cortex, and partial or complete obliteration of the lamina dura, Stafne and Lovestedt (1960) and Chatwin (1962). These changes are distinguishable to the osteoporosis of senility, post-menopause, or disuse in that the lamina dura becomes very thin, but is discernible in the latter conditions mentioned.

These changes are seen not only in organic disease of the anterior pituitary of adrenal glands, (Cushing's Disease and

Syndrome) but also in cortisone (and other corticosteroid) therapy, and corticotropin (ACTH, etc), therapy over prolonged periods. However, not all corticosteroids cause these changes. Applebaum et al (1961) administered massive doses of two new corticosteroids, triamcinoline and triamcinolone acetamide, on normal rats and monkeys respectively, and found no changes in the oral mucosa, jaws teeth or surrounding soft tissues.

Differential Diagnosis of Cushing's Syndrome.

Diagnosis is usually possible at first glance in advanced cases. In milder forms the following conditions must be considered;

1. Simple obesity with hypertension which is sometimes familial. Chemical tests distinguish Cushing's Syndrome.

2. Obesity and hirsutism in women which is occasionally associated with hypertension. Blood count, and chemical test carefully conducted distinguish it.

3. Thymic carcinoma, is rare, but may cause obesity, hypertension, and hirsuitism as in Cushing's Syndrome. These tumours may elaborate a adrenocortical stimulating hormone accounting for the clinical picture. Differentiation is by finding the tumour. (see "Thymus").

Treatment.

1. Inhibiting radiograph therapy to the pituitary, is occasionally helpful in cases caused by adrenal cortical hyperplasia, secondary to pituitary overactivity, Irradiation after unilateral adrenalectomy occasionally gives permanent relief.

2. Bilateral sub-total adrenalectomy should be done if there is no benefit from irradiation. Complete removal of one, and four fifths of the other adrenal gland is the usual procedure and it is quite safe if the patient has been prepared pre-operatively, and is carefully watched during operation and after, and is maintained on replacement therapy with cortisone or hydrocortisone. Recovery may be slow and mortality is not negligible. Pituitary tumour growth has been reported occasionally after total removal (which is sometimes done in an attempt to permanent cure).

3. Extirpation of definitely established adrenal cortical tumour. Replacement therapy is necessary till the other gland is reactivated from a state of "hibernation" to normal function.

4. Testosterone and oestrogen preparations are useful in correcting osteoporosis. The osteoporosis usually departs on correct treatment.

5. Destruction of the pituitary by surgery, electrocoagulation, irradiation by yttrium, or by aplha particles from the synchrocyclotron, has produced striking improvement in some cases, in spite of the ensuing hypopituitarism, which can be adequately treated.

6. Chemotherapy with o,p' DDD, to surpress hypersecretion in hyperplastic adrenal cortices, has been recently tried with promising results. Lisser and Escamilla (1962).

Prognosis. is poor in untreated Cushing's Syndrome due to complication of hypertension and diabetes. Adequate treatment improves prognosis.

Lisser and Escamilla (1962), Peterson (1962) remarks that current medical therapy however, has not been successful in the management of syndrome.

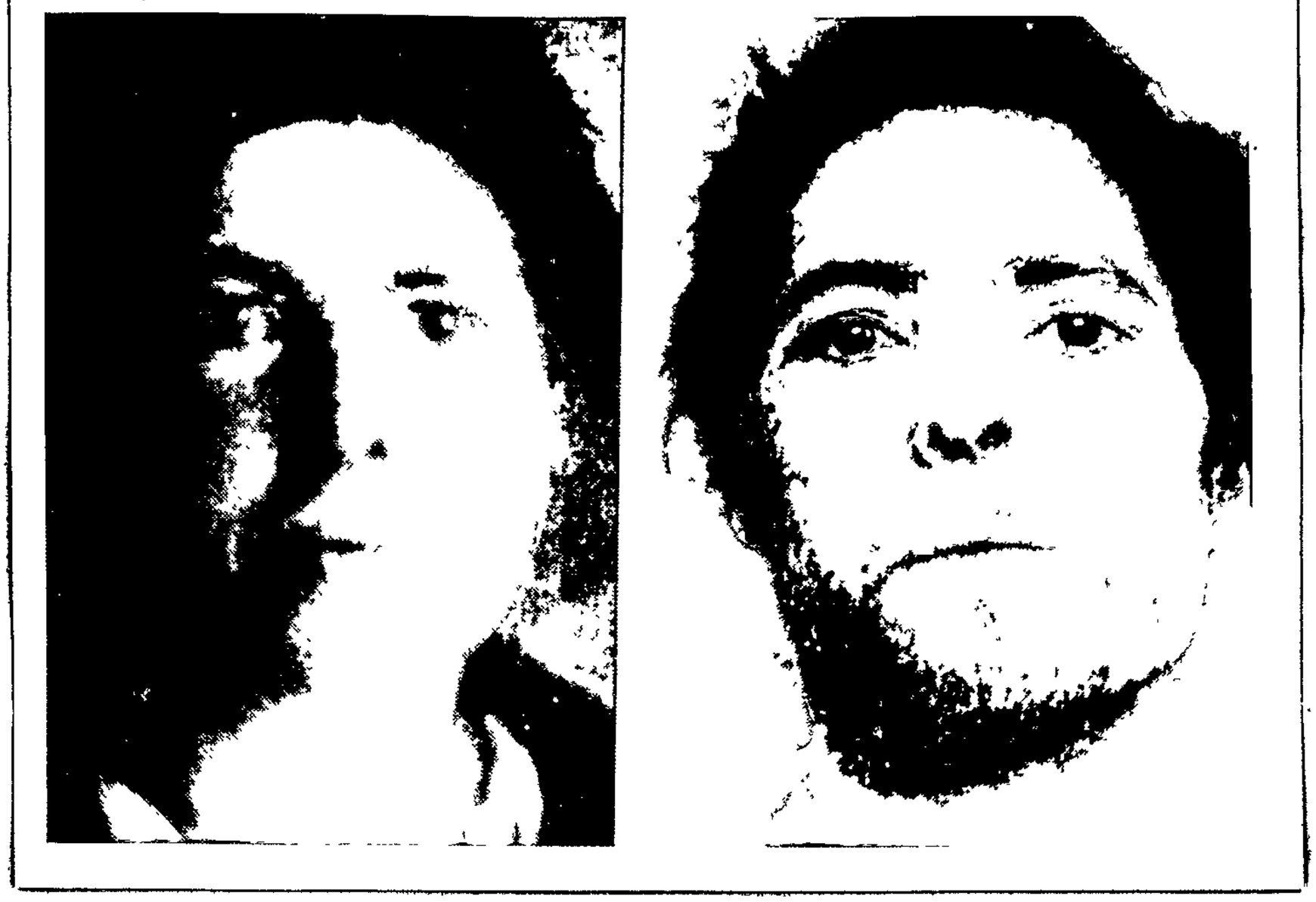

Fig. 24

Adrenogenital Syndrome (hirsutism and virilism) in adult female. Photograph 1 at age 15yrs. before onset of symptoms. Photograph 2 three years later, showing hirsutism and loss of weight.

Lieser and Escamilla (1962).

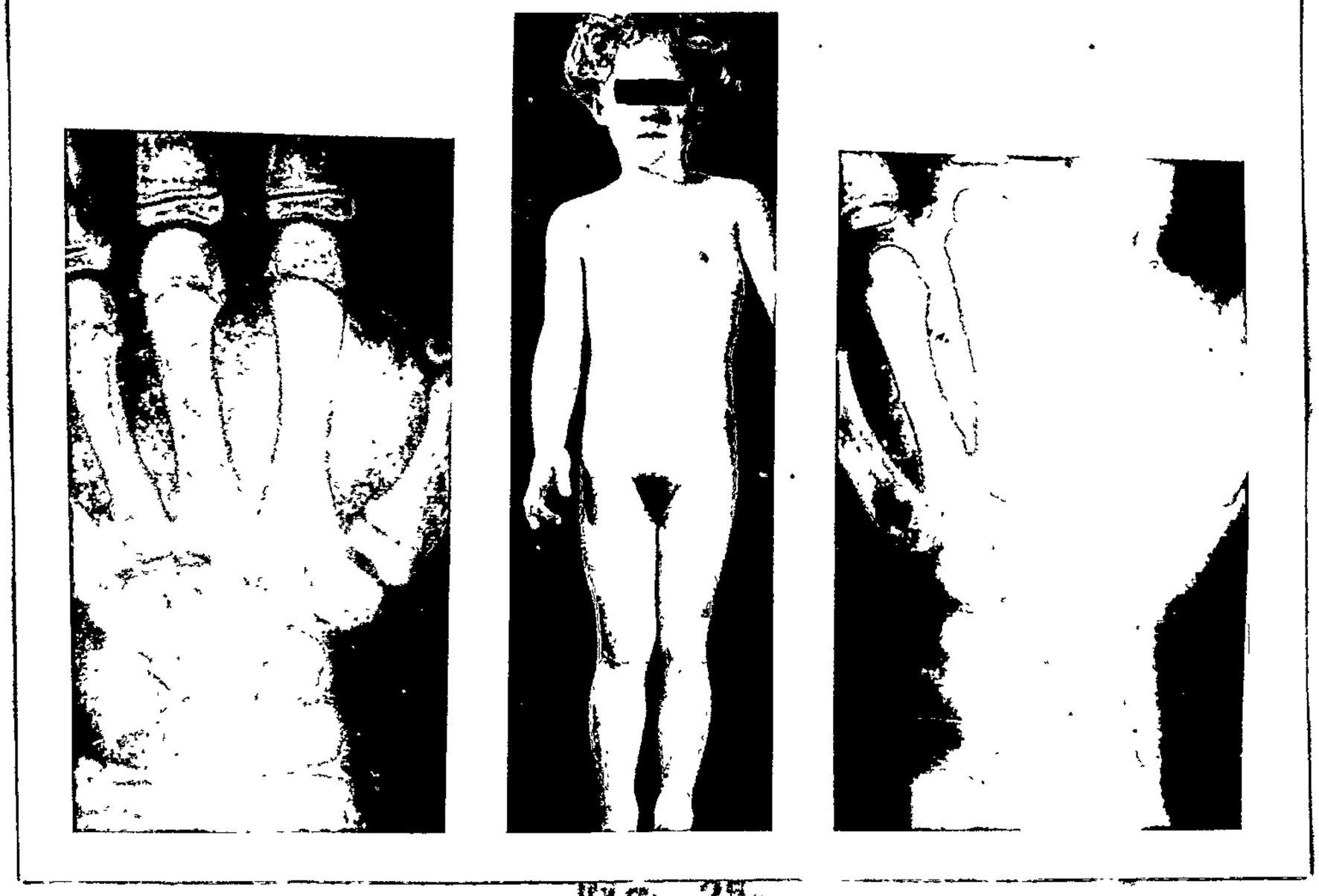

Fig. 25.

Adrenogenital Syndrome. Sexual precocity due to adrenal cortex tumour in girl aged 3yrs. 4mths. Photographs 1 and 3 show a normal and the abnormal wrist development respectively. Bone age 9yrs.

Thoma and Goldman (1960).

FIGURE 1

FIGURE 2

Fig. 26.

Cushing's Disease, in a 23 yr. old male. Typical Cushinoid obese face. Radiographs show considerable reduction of lamina dura, and increased radiolucency of the alveolar bone. Chatwin (1962).

Fig. 27.

Cushing's Disease, treated by removal of one adrenal followed by pituitary irradiation. Age 20yr prior to treatment. Note obesity and plethoric moonface, and beard, and heterosexual hypertrichosis. Photograph is same person 8 years after pituitary irradiation. Loss of 40lb. weight.
Linser and Escamilla, (1962).

ADRENOGENITAL SYNDROME, ANDROGENIC TYPE.

This is another variation of adrenal cortical hyperfunction dominated by ~~a~~drogenic developments in either sex, supposedly caused by an excess of anabolic sex hormones from the adrenal cortex. This is due to hyperplasia of the adrenal cortex, adenoma, or carcinoma of the adrenal cortex. One type of hyperplasia is congenital (familial)-congenital adrenal syndrome, female pseudohermaphroditism, male sexual precocity) and is evident at birth. Masculinisation of the female infant has been caused by administration of progesterones, androgens, oestrogens during gestation. It is thought by some, to indicate an unusual metabolic conversion of 17-ketosteroids in the mother. Lisser and Escamilla (1962).

Clinical Findings;

These vary considerably depending on the age of the onset. Also there are many degrees of the condition, some even resembling Cushings Syndrome called the Mixed Type (including Archard-Thiers Syndrome or"the diabetes of bearded women") Selye (1949), Lisser and Escamilla (1962).

The main characteristics of the androgenic type of adrenogenital syndrome are;

1. Sexual precocity in boys, including growth acceleration and initial tallness, but it slows down later due to early epiphyseal closure resulting in shortness.
2. Pseudosexual precocity with masculinisation in girls, with similar effect on growth as in boys.
3. Virilism with hirsuitism (defeminisation and masculinisation) in adult women. No skeletal changes.

Laboratory Findings;

These are somewhat similar to all three types.

1. Urinary 17-ketosteroids with tumours. Excretion is increased reaching level of 1000mg/24 hours. (normal in preadolscent

children is under 5mg/24 hours., and in adult women 5-15mg/24 hours) An increase in beta fraction of ketosteroids to over 50% indicates carcinoma, and moderate levels suggest hyperplasia.

2. Abdominal x-ray films to show tumour of the adrenals.

3. Extraperitoneal pneumography (retroperitoneal oxygen) is very helpful in demonstrating a small tumour, or in illuminating bilaterally enlarged adrenals.

4. Glucose tolerance tests may show a diabetic type, as in Cushings Disease.

5. Urinalysis, may show glycosuria as in Cushings Disease.

6. Allen test for dehydroisoandrosterone is usually positive, if a tumour is present and helps to distinguish from hyperplasia.

7. Presence of appreciable quantities of pregnanetriol in urine is more suggestive of congenital hyperplasia.

8. X-ray films may show an accelerated dentition in children, Lisser and Escamilla (1962).

Changes in the Oral Region;

If the disease begins early premature eruption of the teeth may occur, Lovestedt (1958), Shafer, Hine and Levy (1963), Lisser and Escamilla (1962) refer to accelerated dentition in children, detected on dental radiographs.

The acceleration of growth initially of the skeletal system is reflected in the oral cavity as elswhere, and so is the final dwarfism that occurs due to early epiphyseal closure. The acceleration of growth in children gives them a much older appearance and precocious moustache appearance occurs in boys, and a moustache appearance also appears in girls sometimes and in adult women, Lisser and Escamilla (1962).

Differential Diagnosis.

A. Of sexual precocity in boys, must involve the consideration of;

1. Testicular tumour, differentiated by discovering the tumour in scrotum.

2. Pineal gland tumour. (see Pineal Gland).

3. Neurogenic sexual precocity, usually due to a hypothalamic

tumour, or following measles or other encepalitis, differentiated by neurological signs of intracranial disease. Mental retardation is usually present.

4. Familial sexual precocity, 17-ketosteroids normal for age.

B. of <u>pseudosexual precocity in girls</u>;

1. Constitutional idiopathic precocity (Novak Type) which is fairly frequent, and is characterised by premature feminine sexual features which are not present in adrenal precocity.

2. Familial or hereditary sexual precocity, differentiated by history.

3. Neurogenic or cereal sexual precocity. (As in boys).

4. Polyostotic fibrous dysplasia, occasionally associated with precocity in girls. Distinguished by additional findings of bony defects, precocity in pigmentation, etc.

C. of <u>virilisation in women</u>;

1. Arrehenoblastoma, masculinovoblastoma or adrenal-rest tumours of ovaries; Pelvic examination reveals ovarian tumour. Urinary 17-ketosteroids normal.

2. Polycystic ovaries (Stein-Leventhal syndrome), also enlarged ovaries.

3. Simple hirsutism is seen frequently sometimes with menstrual disturbances 17-ketosteroids may be elevated and if so, can be reduced and the hirsutism, etc, by prednisone administration. Lisser and Escamilla (1962).

<u>Treatment</u>.

1. Adrenal cortical tumour; surgical removal imperitive, as it may be a malignant adenoma or carcinoma. Some hirsutism may remain following this but menses is usually restored, and sometimes fertility.

2. Hyperplasia: Cortisone surpresses the overactivity and restores normality; 50-100mg daily, but later can be reduced. Formerly girls with large build, and large clitoris were raised as boys, with plastic reconstruction, of a satisfactory penis, and excision of the ovaries and uterus, but with the advent of cortisone therapy, has been abandoned and feminisation been substituted. Blizzard

and Wilkins (1957), Lisser and Escamilla (1962).

3. Psychological care.

4. Removal of excess hair in females.

5. Oestrogens occasionally used in women. Lisser and Escamilla (1962

Prognosis.

Is good, if correct treatment is instituted. Malignancies can also be successfully treated if they have not broken through their capsule, metastases can also be hormonally active and may appear several years after excision of an adrenal carcinoma. Lisser and Escamilla (1962).

ADRENOGENITAL SYNDROME, OESTROGENIC TYPE.

Occasionally gynaecomastia is found in males, but it is relatively rare, and in most cases occurs in adults. By August, (1957), 34 cases had been reported. Hormonal tests show an increased urinary excretion of oestrogens, but 17-ketosteroids are normal.

Wilkins (1948) reported a case of a boy aged five, with cure following removal of an adrenal cortical adenoma. The boy's bone age was ten years. This would have had its effect in the oral region.

Treatment and Prognosis is similar as for androgenic type tumour. Lisser and Escamilla (1962).

PRIMARY ALDOSTERONISM (Conn's Disease).

Aldosterone, the most recently discovered adrenal secretory substance, is a highly potent sodium retaining substance, which remains after extraction of the other corticosteroids. It was first called "electrocortin" in (1952). It is probably secreted due to ACTH stimulation Cope and Garcia-Lanrado (1954).

It has been isolated from the urine of oedematous nephrotics, cardiacs with congestive failure, patients with decompensated hepatic cirrhosis, and women with enclampsia, and in such cases, it is called, Secondary aldosteronism.

Due to the stress of major operations, there is also a rise in aldosteronism for about 24 hours, and it is called "postoperative transient aldosteronism".

Primary aldosteronism is the name given to the hyperaldosteronism due to an adrenal cortical adenoma (70%), bilateral hyperplasia (10%), and carcinoma (5%) Conn and Louis (1954-55) first described the syndrome. Up to (1960) at least 200 cases have been collected, Conn (1960).

Clinical Features.;

These are; arterial hypertension without oedema, weakness, headaches, muscular spasms, polydipsia, polyuria, nocturia, cardiac enlargement in some, paresthesias of face and extremities and dryness of the mouth.

Laboratory findings are a high urinary aldosterone level, low serum potassium, high serum calcium, normal 17-ketosteroids in all cases so far reported.

Changes in the Oral Cavity.

These are; dryness of the mouth due to the polyuria, and paresthesia of the face. In three case histories reviewed, a beefy-red tongue was reported in one, and in another the primary complaint was of throat trouble for a three year period (described as sluggishness), Resch (1958), Lisser and Escamilla (1962).

Treatment.

Is surgical removal of adrenal tumour, or bilateral adrenalectomy in absence of a tumour, with replacement therapy, Lisser and Escamilla (1962).

STRESS AND THE "ADAPTATION SYNDROME"

Hans Selye (1948, 1949, 1950-56) made extensive studies on the matter of stress and its bearing on the adrenal gland. He formulated a theory of response to prolonged stress as part of the individual's adaption which may lead to a clinical entity, which he called the "General adaptation syndrome", The chief changes seen in this syndrome, he states, are enlargement of the adrenal cortex, with increased cortical hormone, involution of the Thymus, and of other lymphatic organs, gastrointestinal ulcers,and certain metabolic changes and variations in the resistance of the organism.

He states that the syndrome evolves in three stages;

1. The alarm reaction, consisting of shock and counter-shock phase,
2. The stage of resistance, which is a protracted counter-shock.
3. The stage of exhaustion, the result of prolonged exposure to stimuli.

In the alarm reaction, the cells of the adrenal cortex, hypertrophies as an active defense against shock, and there is increased secretion of corticotrophin and corticoid.

Many wasting diseases cause atrophy of the adrenal cortex, and loss of adrenal lipid, and Selye suggests that it is due to the prolonged stress, with mobilisation of the lipids and ultimate exhaustion and atrophy of the adrenal glands. Apparently, the hormones of the adrenal cortex, are necessary for cellular enzymes to catalyse the energy producing processes of cells.

Some question Selye's theory but much investigation is still proceeding following Selye's reports, and there is much to commend it. Sayers (1950) gives an excellent review of the literature on the subject up to (1950).

One interesting feature of the syndrome described by Selye (1949) is that somatic growth is inhibited during stress, especially during the alarm reaction and stage of exhaustion. He suggests, that this may be the cause of the osteoporosis caused by systemic stress, and is possibly due to a supression in the growth hormone together with excess corticotrophin. Albright and Reifenstein (1949)

gives an account of the osteoporosis associated with the stress reaction.

In recent years, Selye (1956), has proposed that his adaptation syndrome concept has explained the relationship between injury and disease, the adjustment mechanism for repair the process of healing and return to health.

Stress may be caused by haemorrhages, injuries, surgical wounds, painful areas, radiation, drugs, nutritional deficiences or psychic trauma. All these factors have a indirect effect on adrenal cortical secretions, and is probably through the Adaptation syndrome theory of Selye. It has been suggested by him, that the sequence of events following, for example, local tissue damage is as follows;

1. The local tissue damage is as follows;
2. The central nervous system which, in turn acts upon,
3. The anterior pituitary to release ACTH; the ACTH, in turn stimulates,
4. The adrenal cortex to increase the anabolism for protoplasm in the nondamaged parts of the body tissue;
5. This latter action releases materials for tissue repair;

Silverman (1961) comments that there are simpler relationships which may have three of these four components, such as a sequence involving the central nervous system, the pituitary gland, and the body tissues. These involve the central nervous system being stimulated by the end organ initially. There is another arrangement which by-passes the central nervous system and the pituitary gland, involving a bipolar relationship between another endocrine gland to secrete and to correct the deficit. This is seen in the activities of the parathyroid and adrenal cortex which produces aldosterone.

Silverman (1961) also states that some of the adrenal hormones such as the glucosteroids (of which cortisone is one), have a direct effect upon carbohydrate metabolism, and may cause a deleterious effect upon an existing disorder such as diabetes. In such a case, Sorrin (1960) remarks that the production of new carbohydrate from non-glucose matter (gluconeogenesis), and the diabetogenic effect of the increased need for insulin will result

in an exaggeration of the body's response to local periodontal insults. Increased doses of cortisone may also cause a negative nitrogen balance, following the increased metabolic effect of this hormone, which can result in osteoporosis affecting the alveolus causing precocious alveolar atrophy.

Prolonged stress conditions will utilise large amounts of ascorbic acid, which is probably necessary for the synthesis of hormones and also for collagen formation. A deficiency of ascorbic acid therefore may result in an interruption of the body's adaptation and delayed healing.

Another important function of the glucosteroids is their inflammatory effect. The elaboration of these hormones under stress and also in therapy may cause a lowering of the protective inflammatory barrier and spread of infection such as in periodontal conditions, Silverman (1961).

Likewise, an increased secretion of the mineralocorticoids due to prolonged stress may cause serum potassium retention and increased sodium and chloride excretion, which will result in a flow of fluids to the cells, and a concomitant oedema having its effect on the gingival tissues. Other changes may lead to hypertension, nephrosclerosis, myocarditis and diffuse collagen diseases.

The point of interest in all these observations is that the stresses that cause the adaptation syndrome and the release of adrenal cortical steroids, may originate in the oral cavity spreading to a general body reaction. Conversely, a non specific stress, such as nutritional deficiences may also cause a general body reaction, and the periodontium may become a target organ.

A tendency toward osteoporosis has been described as a result of hormonal changes induced by stress, Albright, (1947), but as Glickman (1958) remarks much yet has to be clarified as to this. The subject is of special interest because of its possible bearing on bone loss in periodontal disease.

Dental Surgery and the Stress Reaction.

A good deal of investigation has entered into this subject which is of considerable interest. Howard et al (1955) studied

adrenal function of soldiers injured in combat during the Korean War. Adrenocortical response of intact glands 24 hours after traumatic stress was characterised by an increased concentration of 17-hydroxcorticosteroids in the plasma, increased excretion of 17-ketosteroids, diminution of circulating eosinophils in the blood, significent sodium retention and diminished sodium excretion, and hypopotassaemia and hyperpotassuria.

Severe emotional stress in patients who are apprehensive, prior to surgical intervention, is an important factor, deserving serious consideration. Strean (1959), Hetzel (1955) reported that urinary 17-ketosteroids in a group of ten healthy subjects rose from a mean level of 1-4 micrograms/minute, while they were tranquil, and 5.6 to 8.3. micrograms/minute when feelings of apprehension, anger, or excitement were present.

Increased adrenocortical activity, . . appears to be a normal physiological accompaniment of surgical operation, Franksson and Van Euler (1954), and Baylis (1955, 1958).

To dentists, particularly oral surgeons, adrenocortical insufficiency imposes an important problen. The life of the patient may be placed in jeopardy if the operator is unaquainted with it. Strean (1959). The symptoms and signs of adrenocortical insuffiiency are varied and numerous but the following would be involved;

1. Slight nausea or malaise,
2. Temperature up to 105^0.
3. Fall in blood pressure.
4. Increased pulse rate.
5. Derrangement of the fluid or electrolyte balance (decreased serum sodium, increased serum potassium).
6. Hypoglycaemia.
7. Shock.
8. Lethargy.

Any one of these signs may be an indication of impending danger, Piro, Yandel and Kutscher (1958).

Savage (1962) states that the adrenal cortex probably secretes some thirty different steroids but only one is important in man, cortisol (hydrocortisone) with a normal output of 25mg diem, and in stress up to 200mg/diem. Adrenal output is controlled from the

hypothalamus which is probably controlled from the level of cortisol in the blood. Normal response to stress, takes the form of an increase of cortisol by the adrenal. In a patient on cortocosteroids we are faced with a different situiation, because the corticosteroids are being supplied artifically, so that the adrenal glands "go to sleep". It involutes, but does not die. There is a great variation in the time required for the adrenal cortex to return to normal function after corticosteroid therapy has ceased, from seventeen days to many months having been reported. Nixon (1962) comments that it may take as long as 24 months. Strean (1959) remarks that approximately 10% of the population (U.S.A.) are receiving some form of corticosteroid therapy. Bilateral surgical adrenalectomy and in some instances medical adrenalectomy have also been carried out with increasing frequeney in recent years for the control of certain types of carcinoma and other diseases (cancer of the breast and prostate particularly). Today there are a number of patients with no adrenal glands, or with atrophied, poorly functioning or non-functioning adrenal glands who must undergo oral operative procedures. The maintence dose of cortocosteroid varies with each adrenalectomised patient, but is usually about 25mg, three times a day, of oral cortisone, Piro, Yandel and Kutschner (1958).

It is generally felt that patients under coticosteroid therapy, require additional corticosteroids to cover the period of stress associated with dental and oral surgery, Blackburn (1955), Piro et al (1958), Strean (1959), Cope (1961), Savage (1962), Nixon (1962). The amount of strain placed on the stress mechanism during dental care, may in fact have been greatly underestimated. It is erroneous to accept that dental treatment is a minor procedure, Piro et al (1958), suggests that the 100-250mg cortisone be given to the completely adrenalectomised patient during the 24 hour preoperative period, and 100-300mg cortisone by mouth or hydrocortisone on the day of surgery. It is always better to err on the higher dosage side.

Strean (1959), in considering the stress phenomenon in relation to surgical anaesthesia emphasises, the importance of ascertainiug whether the patient is on steriod therapy and if that therapy has

been abrupt withdrawn prior to the examination. The superimposition of surgical anaesthesia (which is a cause of major stress), upon the abruptly withdrawal of corticosteroid therapy can precipitate an adrenal crisis and death within a very short time. He adds that corticosteroid therapy should be reinstituted in such cases before surgery is contemplated, and if there is to be an emergency, operation , the patient should receive 100mg hydrocortisone infusion concentrate in saline during and immediately after the operation (alternative is 5-10mg sol. hydrocortisone hemisccinate or prednisoline phosphate). This should also be given if an adrenal crisis occurs.

Savage (1962) states that for a normal dental operation 100mg cortisone or 25mg prednisolne should be given by injection 24 hours and two hours pre-operatively and at the end of the operation. For a minor operation the oral dose should be doubled for two days. Wounds heal normally. He adds that an increasing number of people are now having corticosteroid therapy and therefore it is necessary always to enquire if the patient is on corticosteroids and never to stop them. Nixon (1962) comments that the patient should be asked if they have had corticosteroids at all in the previous two years. If it has been discontinued before that period supplimental therapy during dental surgery is necessary. He states that patients on corticosteroid therapy are major anaesthetic risks. Adrenal collapse is treated by 100mg hydrocortisone hemisuccinate intravenously.

Robinson (1963) in commenting on the report of Savage (1962), and Nixon (1962) remarks that those who warn against the dangers of oral surgical and other dental procedures to patients receiving corticosteroid therapy are not alarmists, but sound advisors.

Shannon et al (1961, 1962, 1963,) carefully studied the effect of stress in dental patients, recently found definite adrenocortical stimulation associated with exodontia, local anaesthesia, oral surgery, and also the effect, different times of the day had on such oral procedures. He stresses the importance of the dentist's responsibility in reassuring the patient, particularly in the initial few minutes of the appointment when much stress usually occurs (1963).

Hypercortisonism and infection resistance and wound healing.

Cortisone is a most useful and often life-saving drug, but should only be administered after due consideration of the possible benefits and side-effects. Successful therapy depends on the co-operation of the patient and careful observation and awareness of the doctor. The side-effects of cortisone therapy may be far more serious than the disease for which it is given. The liability to delayed healing and the tendency for local pyogenic infections to become generalised are of special interest in this regard. Surgical procedures, including dental, must be undertaken with consideration and care and with adequate antibiotic protection in patients who are taking cortisone. This applies especially to patients with rheumatoid arthritis or rheumatic fever, for the dangers are very real. Blackburn (1955).

This phenonenum, was first noticed soon after cortisone and ACTH therapy was introduced. Since then a number of careful experimental studies were carried out in which it was shown that in patients receiving ACTH or cortisone, the growth of granulation tissue was inhibited apparently because of inhibited proliferation of new fibroblasts and new endothelial sprouts and because of a depression of the inflammatory reaction. There is apparently, not a supression of mesenchymal activity but rather a delay in the mesenchymal reaction, Shafer, Hine and Levy (1963).

An experimental study by Shafer (1954) on the healing of extraction wounds in rats receiving cortisone showed that the healing of such wounds is delayed.

Ostrander (1958) warns as to patients under adrenocortical steroid therapy, having dental treatment, because of the lowered body defences. He states that it may manifest itself in an acute alveolar abscess developing unnoticed without early symptoms, and signs.

Cope (1961) comments that the view that steroid therapy tends to reduce the body's resistance to bacterial invasion is well founded, and the problem frequently arises of the patient with bacterial disease who needs replacement therapy. Addison's Disease

with active tubercle of the lungs or adrenals is perhaps the best example. In such circumstances maintanence therapy, which aims at merely replacing normal adrenal production, is likely to improve rather than reduce the patient's resistance. It is excessive dosages, such as may be needed for therapy of some diseases, which reduce bacterial invasion.

In view of the above remarks, it is necessary that patients receiving cortisone should be carefully evaluated by the dentist before he carries out oral surgical procedures.

These effects on wound healing, do not occur, according to experiments, on the administration of pituitary growth hormone, and thyroid hormone, (neither does hypopituitarism or hypothyroidism), but there is delated wound healing with hypoinsulinism which has been considered, Shafer, Hine and Levy (1963).