THE MENOPAUSE CLIMACTERUM, POSTMENOPAUSAL SYNDROME.

This is due to diminished ovarian activity, (hypogonadism), and is accompanied by physical and emotional upsets of varying degrees. Selye (1949), Lisser and Escamilla (1962). It can occur both naturally and artifically (due to surgery or irradiation). It usually occurs naturally between the ages of 40 and 55 years, but may occur very early and very late. Menopause means "monthly pause ", and is therefore a misnomer, whereas climacterum means "rung of a ladder", and thus donates a step like progression from middle age to senescence, Lisser and Escamilla (1962).

The most characteristic symptoms, flashes, or sudden wave of heat, drenching sweats, and nervousness - originate in the autonomic system. Frequent also are emotional mental changes, irritability, fatigability, melancholia and crying spells. Other symptoms include palpitation, vertigo, headaches, and arthralgias. Some, or all, of these may become manifest before the cessation of the menses. Prolonged intervals, diminished flow, and menorrhagia often proceed actual termination and may last some two years. Physical changes are gradual, progressive and variable, and include atrophy of the vulva, vagina, uterus, tubes, ovaries and breast. Most women tend to gain weight, though the opposite occurs sometimes, with a loss of elasticity, and wrinkling of the skin. Gradual thinning of pubic, axillary, and scalp hair, may also appear. Massler (1951), Lisser and Escamilla, (1962).

The physical and emotional symptoms may be extended from one to ten years, after the menopause and is called the post-menopausal syndrome. Fertility may occur for some time after the menopause and many instances have been noted, Massler (1951).

Endocrine changes that occur not only involve hypogonadism, but also increased gonadotrophic hormone, in the blood and urine, increased activity of the adrenals, and possibly hyperthyroidism early in the climacteric followed by hypothyroidism later. Goldheizer (1939), Selye (1949).

Differential diagnosis must be made between this and

psychoneurosis and hyperthyroidism. (therapy with oestrogen or antithyroid drugs will soon distinguish). Lisser and Escamilla (1962)

In the male, occasionally a similar syndrome occurs, called the "Male climacteric", with similar psychic, vasomotor, constitutional changes and reduced sexual function, Heller et al (1944, 1948), Lisser and Escamilla (1962).

Oral Manifestations during the Climacteric.

These may frequently occur, Landa (1945), Richman and Arbanel (1943), Ziskin and Moulton (1946), Massler (1951). The chief manifestations which have been described, are changes in the oral mucosa and gingivae (chronic desquamative gingivitis) and osteoporosis

Thoma and Robinson (1955), remarks however, that often the menopause is given to blame for symptoms which have local origons, and cites an illustration.

Changes in the Oral Mucosa.

The mucosa of the nasal and pharyngeal cavities often show the same changes as that of the vagina in that it becomes thin, poorly nourished, and easily traumatised and develops a generalised atrophy Thoma and Goldman (1960), Ziskin and Moulton (1948), also state; that the oral mucosa becomes thin, is easily injured and is vulnerable to infection. Engel (1952) says the gingivae often becomes pale and anaemic and greyish-white patches appear, similar leukoplakia.

Massler (1951), found : the presence of occasional herpetic lesions in 63 out of 86 he studied during the climacteric, and in 34 there was a recurrent herpetic gingivostomatitis. These lesions healed slowly, and have been confused with pemphigus.

Burning sensations in the mouth and glossodynia have been noted frequently, Massler (1951), found that of the 86 patients he studied during the climacteric, 80 had this condition. Sixty three had glossodynia, 31 burning buccal mucosa, and 50 had burning and itching gingivae. Landa (1939), also observed and studied these changes and found that most of the patients wore dentures, and many attributed the oral mucosa changes to the material of which the

dentures was made. Change of material however, did not bring relief. The burning in these cases were often on the palate and upper lip, or the whole mucosal area. About half of the patients were annoyed by the feeling of dryness in the mouth, due to diminished saliva secretion. Some would use a wet handerchief to keep the lips moistened. Loss of apetite often followed in these cases and loss of weight. Hassler (1951), commented that many of the patients he studied attended the clinic because of complaints about their dentures and they often incriminated the dentures because of the discomfort, sores, and abnormal taste sensations they experienced. It could be shown to be incorrect, by the fact that vitamin or oestrogen therapy caused the disappearance of the symptoms.

Atrophic glossitis similar to the type seen in Vitamin B deficiency could be observed clinically in most of the cases Massler (1951) studied. It is not known whether this is due to dietary neglect, or secondary to the low oestrogen levels.

Trott (1959), summarises the results of the experiments of Ziskin et al (1935, 1936, 1938, 1940, 1941, 1947) and states that it appears that both male and female sex hormones, however they are administered, stimulate the production of keratin on mucosal surfaces if the organs producing the hormones are removed, tissue degeneration takes place, but whether this takes place in the epitholium, the epithelial connective tissue boundary, or the corium is difficult to say. Similarly the exact type of degeneration that takes place, would appear to be uncertain.

Gingival changes that occur during and after the menopause are rarely seen, primarily because so few people have their own teeth after the ages of 40-50 years because of their rarity they may be overlooked or confused with other conditions. Trott (1959).

Stones says (1954), the gums are "raw and painful" which is a characteristic symptom. Glickman (1958) described the clinical features as a reddish discoloration of the gingivae which presents a patchy distribution. The surface of the gingivae is usually smoothe and shiny, and when it is massaged with a finger, there is a pooling off of the epitholium, (desquamative gingivitis).

As to the abnormal taste sensations which sometimes appear, Hassler (1951), found this symptom in 62 of the 86 patients, he studied. He said it usually presented a salty, peppery, and sour taste sensations. The patient did not enjoy her meals and did not eat regularly, resulting in malnutrition.

Hassler (1951), refers to another common subjective symptom which often occurs and that is cancerophobia which may be conspicuous and intense. It may be even subconscious, and when it was made conscious, and the patient reassurred, the other symptoms were greatly reduced.

Chronic Desquamative Gingivitis (Gingivosis)

Shafer, Hine and Levy (1963) use the more modern designation of the condition, gingivosis, which they state is apparently a degenerative disease of the gingivae. They state that it occurs in both sexes at any age from the teens to later life, but is predominent in women in the age group of 40 to 55 years, particularly, in those who are subject to hormonal irregularities incident to the menopause. Thoma and Goldman (1960), remark that it is usually seen in postmenopausal women, and in women with gynaecological disorders, and that it is also occasionally seen in aged men.

As early as (1887), it was observed by Tomes and Tomes but no connection with the menopause was considered. They noticed that some types of chronic inflammation occurred in the gingivae in poor middle aged females, in whom menstruation was becoming irregular or had ceased. Instead of the gingivae becoming thickened, and irregular, as it does in ordinary chronic gingivitis, it assumed a mottled-red smooth, polished surface, associated with pain. Their treatment consisted of administering an aperiant. Thomas and Charles (1897) and Magitot (1860) also described this condition.

Prime in (1932) defined a similar condition as a chronic inflammation characterised by diffuseness and desquamation of the gingivae. He reviewed twelve cases, he had seen in twenty years, and noticed that they occurred most frequently during the menopause, more rarely seen on the palatal mucosa and never in edentulous mouths. The patient's chief complaint was burning of the gingivae with hot foods. Histologically the stratum corneum was almost entirely

desquamated, while there was an excessive fungoid growth of the papillae, and marginal inflammation on the labial surface of the gingivae. Merritt (1933) also described this condition of desquamation, redness and mottling of the gingivae in the maxillary and incisor region as pedunculated fungoid appearances of the gingivae. The desquamative condition of the gingivae is preceded by small elevated blisters filled with watery fluid, which break and leave a raw painful surface. This sounds very similar to herpetic lesions which also occur in the postmenopausal syndrome, but which is not true desquamative gingivitis. Sorrin (1940) described another case and made observations similar to those of Merritt and Prinz.

Ziskin and Silvers (1945) report a case of chronic desquamative gingivitis associated with lichen planus. Lichen planus produces similar lesions to chronic desquamative gingivitis and needs to be differentiated from it. Trott and Wade (1954).

Hutchinson and Deewar (1954), also presented a case of a woman who complained of burning sensations in the gingivae and bleeding gums. On the labial surfaces of the upper and lower segments, anteriorly there were extensive, shiny, denuded, red areas.

Engel, Ray and Orban (1950) in an excellent paper described the pathogenesis of chronic desquamative gingivitis. (see under Histopathology).

Glickman (1958) classifies the condition into three groups as follows;

1. Mild form, a diffuse erythema of the entire gingival mucosa. Normal stipling is diminished otherwise there is no pathologic change and no symptoms.

2. More marked form with reddish discoloration in patches, smooth surface. Massaging the gingivae with the finger is attended with peeling off of the epithelium, with an exposed underlying connective tissue surface. The remaining oral mucosa is smooth and shiny. This condition is most frequently seen in the 30-40 age group. The patients complain of a burning sensation in the mouth, and there is marked sensitivity to thermal changes, and to the slightest irritation

3. Severe form; characterised by an appearance of scattered, irregularly shaped and denuded areas. The epithelium in the

remaining portions is greyish in colour and very friable and easily removed. It is extremely painful and sensitive.

However, McCarthy, and Shklar (1960) remark that there is considerable doubt as to the specificity of the losion described as chronic desquamative gingivitis, with a specific aetiology and histe-pathology. They studied 40 cases in the previous twelve years, similar to those described above. In seventeen of these cases the gingivitis appeared as part of a generalised mucosal involvment, including oral and other mucous membranes. In these cases the chronic desquamative gingivitis was an oral manifestation of benign mucous membrane phemphigoid. Four cases were associated with lichen planus. It may also present as an early manifestation of pemphigus vulgaris. They only found three cases associated directly with the menopause which they said was rare. These three cases were very resistant to therapy. They concluded that chronic desquamative gingivitis is not a specific entity but rather a nonspecific gingival manifestation of a variety of systemic disturbances, some of which are better understood than others. Robinson (1962) commenting on these observations remark that it is probable that most oral pathologists and periodontists agree that chronic desquamative gingivitis has a specific aetiology. He considered it as a vesicular gingival condition, caused by stress of one form or another including imbalanc of oestrogenic hormones, allergy and psychological factors.

The aetiology therefore is still uncertain, Thoma and Goldman (1960). It seems clear however, that the sex hormones are involved particularly from the experiments of Ziskin et al (1935-1947). Despite this presumptive evidence a specific relation between gingivosis and the sex hormones has not been definitely established Shafer, Hine and Levy (1963).

The <u>histopathology</u> of chronic desquamative gingivitis has been carefully described by Engel, Roy and Orban (1950), who showed some interesting pathological features by staining sections by the PAS methods. They found an alteration of the basement membrane, or its absence, as indication of the depolymerization of the highly polymerized ground substance components. The epithelium peels off easily because the cementing substance of the cells and the cementing

function of the basement membrane and ground substance have been lost, reduced in amount, or become altered. They found that the ground substance contained increased amounts of water soluble glycoprotein and water soluble but alcohol insoluble glycoprotein and water soluble but alcohol insoluble glycoprotein residues, Foss, Grupe and Orban (1953), also give a report on the histopathologic, and other features of gingivosis.

Shafer, Hine and Levy (1963) commenting on the histologic changes state the epithelium is thin, and atrophic. Rete pegs are short or absent, and epithelial oedema is often present. The basal layer nearly always appears disrupted, and there is infiltration of the epithelium by inflammatory cells. They remark however, that the microscopic findings are not pathognomonic.

Postmenopausal Osteoporosis.

This is a serious complication of the menopause and may lead to spontaneous fractures of the vertebral column, Lisser and Escamilla (1962).

Albright and Reifenstein (1949), remark that it is the commonest form of osteoporosis; and is also the most common of all systemic osteopathies.

It has been described by Albright, Smith and Frazer (1940), who studied 42 cases (40 women and two men), and changed its name from idiopathic osteoporosis to postmenopausal osteoporosis. Cohn (1948) wrote that senile osteoporosis may connect with hypogonadism because of its incidence, together with diminished steroid hormone production in old age. Albright et al (1940), found that in three of his patients, oestrogen therapy produced a markedly positive calcium and phosphorus balance. The experiments of Keyes and Potter (1934), and Pfeiffer and Gardner (1938), found that male doves had bones more osteoporotic than female doves and that they responded to oestrogen therapy.

The osteoporosis affects principally the spine and the pelvis, and to a much lesser extent the long bones. The skull is the least affected. Cohn (1948) noticed that young women who had induced menopause through surgery or irradiation had developed severe alveolar atrophy round the teeth, and believed that it was due to

deprivation of oestrogen, Thoma and Goldman (1960).

Lovestedt (1958) remarks that the opportunity to observe postmenopausal osteoporosis is present in every dental practice, and because of its common occurrence, is the form of osteoporosis a dentist will observe most frequently. Due to the contrast it is more obvious when teeth are present on radiographs.

Treatment of the Climacteric Patient.

Treatment of chronic desquamative gingivitis is palliative in nature and in some cases oestrogen therapy is indicated. In order to keep the patient comfortable, hot rinses containing a tablespoonful of Karo are recommended. Hydrocortone dental ointment is effective in some cases, Thoma and Goldman (1960). Prinz and Green baum, (1939) advocate a rinsing solution of 50 percent glycerine and water flavoured with lemon to relieve the burning sensations.

Speert (1948), showed that both the steroid and synthetic hormones can be absorbed, by the oral mucosa in functional quantities. He also stated that the relationship between oestrogens and cancer has not been clearly established in man as it had in mice but in the absence of more precise knowledge on this subject a properly conservative attitude demands that prolonged oestrogen administration whether local or general, be withheld from patients with a personal history of cancer of the breast or uterus, with a strong familial disposition to cancer or with a precancerous genital lesion.

Glickman (1958) gives the dosage and methods of administration of oestrogens and testosterone. The oestrogens can be applied topically by local injection, or systemically by orally or parenterally Testosterone may be administered either topically or systemically, by the oral route. Trott (1959), states that the oestrogens should be only used when the dentist is satisfied beyond reasonable doubt that the changes in the gingivae are primarily dye to as hormonal dysfunction, and not to some other condition. Consultation with a physician is advisable in such cases before treatment is commenced with oestrogens.

Robinson (1962), states that he has had some limited success with topically applied corticosteroids and reassurance of the patient

McCarthy et al (1960), remark that topical hormone therapy is not of much help, and suggests that until the patient's physiological makeup adjusts itself, management is a problem. Avoidance of irritative therapy and rigorous oral hygiene are always of some help.

Rickman and Arbarbanel (1943), found that 25 climacteric cases following treatment with oestradiol dipropionate administered by injection under the mucobuccal fold showed cessation of symptoms of burning and dryness of the gingivae and increased salivation. Van Minden (1946), used ointment containing oestrogen three times daily on a patient aged 67 with a resultant relief of the symptoms within three months. However complications occurred. Massler (1951) recommends sedative treatment , endocrine sunstitution in severe cases, and vitamin therapy (vitamin B and E). Rational therapy should include a good deal of reassurance and sympathetic understanding by the dentist. Massler (1951), Lisser and Escamilla (1962) and others support this view, that oestrogen should only be given in severe cases, and then administered carefully in cycles, to prevent undue vaginal bleeding. Androgens may also be used carefully but virilism has to be watched. Meprobmate is suggested as a sedative but the barbiturates are probably better.

Armstrong and Hennemann (1956) advocate treatment of postmenopausal osteoporosis with oestrogens and androgens. Albright suggests oestrogen alone.

EXPERIMENTAL HYPERGONADISM AND HYPOGONADISM.

Studies have been made on the effects of gonadectomy and sex hormone administration on animals to observe the effects on the alveolar bone, gingivae, tooth development, caries incidence, and the salivary glands.

Alveolar Bone:

In young mice injection of oestrogen produces proliferation of new bone with filling of the medullary spaces and cavity, and sclerosis through growth of the bone, being inhibited, Kendall (1941), Gardner and Pfeiffer (1943). Urist et al (1950), reports that growth of the condyle is retarded in young kittens by injecting very large doses for six weeks to six months. The thickness of the condyle is considerably reduced of the layers of hypertropied cells of the cartilage. In addition, due to reduced appositional activity, growth is also retarded on the surface of the mandible and maxilla at the sutures, Rushton (1948).

Keyes and Potter (1934), found that the bones of male doves, are osteoporotic compared with those of female doves. Pfeiffer and Gardner (1938) demonstrated that oestrin therapy in male doves produces a marked increase in the density of the bones by stimulation of the oesteoblasts. Albright and Reifenstein (1949), remark that oestrogen apparantly stimulates endosteal bone formation in pigeons and mice, and that testosterone enhances this action in pigeons but inhibits it in mice.

Stahl et al (1950), found that after the administration of oestrogen, the alveolar bone of the rat does not show osteoporotic changes, while that of the mice reacts as do all other bones. Urist et al (1960), found that the effect of oestrogen varies with species and with the different areas of the skeletal system. They found that in mice, the areas of most rapid growth were the ones mostly affected and in old animals the response was delayed.

Nutlay et al (1954) investigating these observations, further found that the administration of oestrogen did not lead to any

changes in the alveolar process in young rats, but in new born mice receiving diethyl stilbestrol or a oestradiol benzoate over a period of more that 25 days, there was a replacement of the haemopoetic marrow of the alveolar process by a fibrous marrow and there was a reduction in the marrow space by new bone formation.

Testosterone has different effects on bone to oestrogen, being instrumental in bringing about epiphyseal closure in some animals but not others, Green (1956).

Hunt and Aub (1956), state that they do not think there is narrowing of the marrow cavities in women during adolescence. Glickman and Shklar (1955), and Glickman (1956) discovered that repeated injections of oestrogen into white mice led to increased endosteal bone formation in the jaws, and they think that it stimulates bone formation and fibroplasia which compensates for destructive changes in the periodontium induced by the systemic administration of cortisone.

Piroshaw and Glickman (1957), found that ovariectomy results in osteoporotic changes in the alveolar bone of young adult mice but has no effect in older mice.

Gingivae.

Ziskin, Blackberg and Slanetz (1935-36), found that subcutaneous injections of oestrogenic hormones in castrated female monkeys produced keratinisation of those areas of areolar mucosa where it does not normally occur and epithelial pearls in the stratum germinavatum. In further experiments however, follutin, (follicular stimulating hormone) produced changes in the gingivae which took on the clinical characteristics of Vincent's infection.

With improved hormonal extracts, Ziskin (1938) showed that oestrone, oestradiol and oestriol produced hyperkeratinisation of normal keratinised layers, and hyperplasia of the prickle cell layer, whereas the gonadotrophic hormones extracted from the urine of pregnant mares reduced the surface keratin and caused hypoplasia of the prickle cell layer.

Ziskin and Blackberg (1940), compared the gingivae from ten normal monkeys with those from three castrated males, four castrated

females and five hypophysectomised females. They noticed that there was evidnece of tissue degeneration, faint staining properties and an altered arrangement of the prickle cell layer, which was more apparant in the hyposectomised female monkeys, than in the castrated ones. In the castrated males however, there was hyperkeratinisation which is similar to the effect following injection of oestrogen.

Later Ziskin (1941), found that testosterone propionate caused hyperkeratinisation and thickening of the gingivae and the hyperplasia produced was proportional to the dosage of hormone injected.

With oestrogen implants the results are much more severe. Ziskin Zegarelli and Slanetz (1947), placed oestrogen implants subcutaneously in female dogs up to five times. After an average experimental period of three months, there are hyperplastic changes in the oral mucosa but after seven months, the blood developed a leucopenia, the uterus and gingivae showed an inflammatory necrosis and there were skin changes. If 3gm of Soya bean lecithin is given in the diet, the toxic symptoms are reduced. Later (1947), they found histologically that for the first six months, there was hyperplasia and thickening of the gingival epithelium by a third and in the corium there was a considerable increase in fibroblasts and collaginous tissue. The ninth month showed oedema and degeneration in the epithelium and connective tissue, and in the thirteenth month total degeneration, necrosis and loss of the epithelium, and a heavy infiltration into the corium with inflammatory cells. Similar changes were observed in the vaginal epithelium. The authors point out that this differs from monkeys and rats where there is proliferation of the tissues and wonder whether or not the degenerative changes seen in dogs are similar to those found in man. Engel (1952), points out that in these experiments of Ziskin et al (1936-47) more emphasis has been on epithelial changes than those of the ground substance. Engel (1952), found that in monkeys receiving oestrogenic hormones an increased amount of alcohol insoluble and water soluble carbohydrate material is found in the ground substance. He postulates therefore that there are two phases in existance at the same time which are in equilibrium; that is a high glycoprotein and low water phase. In

oedema for instance, it is felt that the water phase predominates and this also occurs in some degenerative conditions.

Trott (1959), summarises the experimental evidence in stating that it appears that both male and female sex hormones, however, administered, stimulate the production of keratin on mucosal surfaces. If the organs producing the hormones are removed, tissue degeration takes place, but whether this takes place in the epithelium, connective tissue-epithelial boundary or in the corium it is difficult to say. Similarly the exact type of degeneration which occurs is difficult to ascertain.

Stahl et al (1950), have shown that oestrogen administration leads to an increase in the number and size of the epithelial attachment of the rat or mice molars.

Nutlay et al (1954), found that the administration of oestrogens did not lead to any changes in the gingival epithelium or epithelial attachment, of young rats. In old mice which received injections or subcutaneous pellets of a-oestradiol benzoate, there was an increased downgrowth of epithelium attachment along the root surface and into the bifurcation of the roots. It appeared in almost a tumour like fashion between the first and second molars. Periodontal pockets and associated root resorption were also present, in the final stages.

The systemic administration of methyl testosterone appears to retard the downgrowth of sulcus epithelium over the cementum, Rushton (1952).

Kluczka et al (1961), made investigations on rats whose gonads were irradiated, noting changes in the periodontal tissues. Macroscopic inflammatory changes were found and tooth mobility.

The Teeth.

Kranz (1912-1914) reports retarded eruption of the cuspids in castrated pigs.

Schour, (1936), reported that gonadectomy in the thirteen lined ground squirrel resulted in disturbances in calcification of the growing enamel, dentine and bone.

Muracciole (1956, 1957), reported pronounced disturbance in dental calcification after gonadectomy. Calcification of the dentine was poor and irregular, and the activity of the odontoblasts was increased in one zone of the dentine and resulted in the formation of dentinal buds, and obliterated the pulp chamber with the disappearance of the organic substances.

Nutlay et al (1954), found that the administration of oestrogen did not cause any changes in the teeth of young rats, but in young mice receiving oestrogen there was root resorption associated with periodontal pockets in the final stages, particularly.

On the other hand, Schour and Massler (1943), Stones (1954), and others, state that there are no changes in the teeth in either experimental hypergonadism or hypogonadism.

Caries.

Keyes (1947), studied dental caries incidence in the Syrian hamster following gonadectomy. There was more caries activity in the males than females in the normal hamsters and gonadectomy reversed this. The males also increased in weight. The average caries scores after a 133 day period; was control males 62.8, control females 20.9, Castrated males 9.5, castrated females 7.2. Keyes (1949), produced further results confirming this reduction in caries incidence following gonadectomy. These results were also confirmed by Shaw (1950).

Muhler and Shafer (1952), and Bixler, Muhler and Shafer (1954), also working on this subject produced a reduced caries incidence following gonadectomy in albino rats.

Gronroos and Rauma (1960), studied the effect of sex hormones on the frequency of caries in the teeth of oophorectomised rats and the most conspicuous result was in the caries incidence increase in oestrogen receiving rats. Progesterone produced a slight increase in caries, whilst the androgens had no effect.

Shaw (1950), also found on working with caries susceptible white rats, maintained on a cariogenic diet, that rats which had completed one or two reproductive cycles had a slightly lower average number of carious lesions, that their littermates, which had never been pregnant.

Salivary Glands.

There are conflicting reports in the literature concerning the effect of castration on the salivary glands. Raynaud (1944), showed that there was a significent loss in weight of the submaxillary glands in mice castrated at birth, and sacrificed at two to three months.

Shafer and Muhler (1953), Muhler and Shafer (1953), have demonstrated a marked diminution in the size and number of granular tubules in the submaxillary glands of rats following either gonadectomy or the administration of oestrogenic hormones.

Sreebny et al (1958), on rats, castrated at 30 days, of age, also found these histologic changes in the submaxillary gland.

Baker and Pliske (1957), found that castration of male rats, resulted in some reduction in weight of the pancreas, but not the parotid gland. This was also confirmed by Sreebny (1960),

Sreebny (1960), also confirmed the earlier result of Junqueira et al (1949), on mice, showing that the protease content of the submaxillary gland was reduced following castration.

Castration had also been proved to lead to a reduction in the proteolytic activity, and the submaxillary gland to about one half. Sreebny (1960).

Flieder (1959), studied the effect of thyroid hormone and testosterone on salivary gland phosphorus and nucleic acid content on male weaning rats and found that the testosterone injected animals showed a marked increase in inorganic phosphate/desoxyribonucleic acid (DNA) ratio, and the residual protein /DNA ratio over the control group.

Klapper and Shackleford (1961), worked on hormonal influences on the acidic carbohydrates of hamster submaxillary mucin, and concluded that the synthesis of the sialic acid fraction of the submaxillary secretion and/or its incorporation in the secretion is influenced by the female sex hormone. A sexual dimorphism can therefore be said to exist in the hamster submaxillary gland, at least in respect to the mucin fraction of the secretion.

THE SALIVARY GLANDS.

Evidence is accumulating gradually that the Salivary Glands, at least in the experimental animal, are associated very intimately with various endocrine organs and that a functional disturbance in one or the other may induce significant morphologic and physiologic alterations in the Salivary Glands.

I have already considered the relation of the Salivary Glands to the endocrine glands under, Experimental Hypopituitarism, Experimental Hypothyroidism, Experimental Hyperadrenocorticism, Experimental Hypogonadism and will now briefly review the literature and present current opinions on the subject.

The first to suggest a relation between the endocrine and Salivary Glands, was Hanau (1926), who advanced the hypothesis that the Salivary Glands participated as and organ in endocrine stimulation. This conclusion was reached because of the palpable bilateral swelling of the parotids of a patient during each of six successive pregnancies. Phillips (1931), made similar observations, during pregnancy and also lactation.

Much of the earlier work in this regard was done by Japanese workers during back 30 years.

It has been reported from various sources, Ogata (1933, 1944)) Ito (1952, 1954), that the Salivary Glands, particularly the parotid, produce an internal secretion which influences carbohydrate metabolism. Most of these indicate an insulin antagonism. Ito, (1960) in his extensive review of the literature on this subject lists 99 references which are mainly of Japanese workers. The collective studies of the Japanese investigators are not entirely convincing, however, in affirming that the Salivary Glands possess an endocrine function in themselves, although some of this work is quite suggestive. Shafer, and Hubler (1960).

Nicholls (1951), states that the secretion of the Salivary Glands is generally known to be under the control of nervous reflexes, affecting the secretory cells, the blood flow and the contractile components of the glands. Several known hormones, secretin, pituitrin

and insulin have been found ineffective as stimulators.

Lacassagne (1940) and associated French workers, showed that there were histological differences between the male and female mouse submaxillary glands and that if the male sex hormone was administered to a female mouse its submaxillary gland assumed the characteristics of that of a female.

Raynaud and Rebeyrotte (1949), reports a difference in amylase activity of mouse saliva, between males and females. Junquiera (1948) however, was unable to verify this but noted changes in protease activity. Buillard and Delsue (1941), and Raynaud (1950) reported changes in salivary glands following castration and testosterone administration respectively. Lacassagne and Chammorro (1940), reported extreme atrophy of the submaxillary glands following hypophysectomy. Arvy and Gabe (195o), showed similar changes following thyroidectomy.

Sreebny (1953-60) confirmed Junquiera's (1948) observations showing that submaxillary gland protease was reduced in mice following castration. He also found reduction in proteolytic activity to about half.

The endocrine relations of the salivary glands was revieved by Volker (1958), in an interesting report.

Shafer and Muhler (1953), found a marked diminution in the size and number of grandular tubules in the submaxillary glands of rats following either gonadectomy of the administration of oestrogenic hormones. Testosterone had the opposite effect.

Shafer and Muhler, (1955), and Clarke, Shafer and Muhler (1956) found that hypophysectomy, thyroid extract and thiouracil all had profound effects on the structure of the submaxillary glands.

The changes in the salivary glands (extreme atrophy of the grandular tubules) following hypophysectomy were the most marked. Replacement therapy with several hormones on such animals, showed no change with insulin, oestradiol, and progesterone had a minimal effect, cortisone and pure growth hormone a moderate effect, thyroxine and testosterone had more effect, and the greatest effect was thyroxine and testosterone in combination, which completely reversed the regressive changes, Shafer et al (1956), Bixler et al (1959).

They also found a corelation between caries incidence and submaxillary gland structure.

Arginase, a salivary gland enzyme, was found to decrease in activity in mouse salivary glands by cortical steroids, but was not influenced by thyroxine. Kochakin et al (1955). Shafer et al (1959) showed an inverse relation between protease and arginase activity in rat submaxillary glands under the influence of varying endocrine dysfunctions.

Bixler et al (1957), found that following hypophysectomy the RNA is reduced markedly in the acini of all submaxillary glands. It was not restored by cortisone but was with thyroxine and testosterone in combination.

Studies have also been made on salivary flow and viscosity in the rat and its relation to the endocrines and dental caries by Shafer et al (1958). Thyroxine stimulates salivary flow while propylthiouracil and thyroidectomy reduce it. Decreased salivary flow is usually accompanied by increased incidence in caries.

Fawcett and Kirkwood (1954), following their experiments on rats, remarked that the evidence conclusively demonstrates that the salivary glands have a major role in the extrathyroidal metabolism of organic iodine in the body and that these organs function as "reverse thyroids".

Albright et al (1954) showed a hypertrophy of the salivary glands following the administration of triiodothyronine for myxedema in the human, and may be of some significence in confirmation of Fawcett and Kirkwood's (1954) work.

However, Muegamer (1955) could not prove these results of Fawcett and Kirkwood (1954) in his experiments on dogs, and concluded that the salivary glands play no part in the metabolism of iodine analogues. Myant (1960) also analysed Fawcett and Kirkwood's results critically, and concluded that thyrotrophic hormone, which stimulates the iodide concentration mechanism in the thyroid, does not affect iodide accumulation in the salivary glands.

Wase and Feng (1956) have presented convincing evidence that sialoadenectomy reduces thyroid activity. The reduced growth rate could be reversed in young animals by administration of bovine thyrotrophic hormone.

Taurog et al (o959), concluded from their experiments that the submaxillary iodide pump, unlike the thyroid iodide pump, is not affected directly by the presence or absence of TSH.

Flemming (1959), gives a good review of the literature, and found in his experiments that parotid gland extract injections in mice affected changes in the growth centres of the femur and in the zone of enamel secretion in mandibular incisors. Flemming (1960), experimenting further found additional evidence on the widespread effect of parotin in experimental animals.

Ogata and Ito (1959), and Ito (1960), supported by many researches of the Endocrinological Laboratory of the University of Gunma, Japan were successful in isolating and defining a biologically active protein occurring in animal and human parotid glands, which they regarded a hormone, and designated it "parotin".

Ito et al (1960) isolated this from cattle submaxillary glands, human saliva, and human and rabbit urine - and named it S-Parotin. Saliva parotin A, and uroparotin, respectively. Full details of the isolation and properties of parotin are given in Ito's extensive report (1960). Parotin has a specific effect on the activities of oral organs and of other parts of the body, they state. It seems to promote the calcification of hard tissues, especially enamel, dentine and cementum of teeth and lowers significently the blood calcium level. It is suggested by them, and also Haim (1959), that the submaxillary gland supports this incretory function of the parotid and that the calcium activity theory of the endocrine function of the salivary glands has been accepted by many authors. Parotin, by resorption, becomes part of the chemical structure of saliva, and the incretory release of the hormone takes place through the lymphatic system.

Ito (1960) claimed that the actions of parotin are as follows;

1. Promotion of the growth of hard and mesenchymal tissues,
2. Lowering of serum calcium by 15-30 percent (calcium activity),
3. Changes in rabbit leucocyte counts following a definite time course (leucocyte activity).
4. Promotion of calcification of incisor dentine in rabbits and rats. (dentine-calcification activity).

5. Effective in the treatment of pyorrhoea and arthritis.

6. And many other actions.

The studies of Imagawa (1958), Flemming, (1959, 1960, 1961), Quinterelli (1961), Sierve and Dal Maso (1961), have supported these findings, that the salivary glands secrete a specific hormone called parotin.

Sieve and Dal Maso (1962, 1963) in experiments carried out at the Stomatological Institute of the University of Milan, demonstrated that glandular overactivity in secreting parotin causes abnormally increased growth of bones and teeth, whereas undersecretion causes impaired calcification and vascularisation of the hard framework of the head including the upper and lower jaws and teeth. Complications resulting from in the inadequate secretion of parotin are improper differentiation of ameoblasts and odontoblasts, and abnormal fragility of some or of all maxillofacial bones, thereby leading to odontoparallaxis and osteodystrophy, conditions which render bones and teeth subject to fractures.

Kraintz (1960) discussed the report of Ito (1960), and remarked that he had hoped that Ito would have presented more documentation proving that parotin is indeed a hormone. Admittedly he said, the salivary glands play a role in calcium metabolism and haemostasis through their exocrine function. Dehails concerning the endocrine role of the salivary glands are not altogether convincing, since the removal of the salivary glands results, in a loss of a turnover mechanism for electrolytes and minerals that may have a direct effect on the function of the systemic mineral metabolism. The studies of the Japanese workers have at least emphasised the role of the salivary glands in carbohydrate metabolism and should stimulate more research.

Gangerosa (1961), made an attempt to prove the alleged actions of parotin as suggested by Ito (1960), but was not able to, in any respect in his study, and concluded that he had no evidence of any hormonal activity of parotid secretion.

Godlowski and Calandra (1960-1962) experimented on dogs to evaluate any possible endocrine effects of normal salivary glands on carbohydrate. The glands were bilaterally removed in one series

and ligated in another series of experiments. The greatest effect was in ligation which resulted in atrophy of the glands, because of the difficulty in complete removal of the parotids. The authors believed that the submaxillary glands secretion /causes inhibition of insulin action. Further investigations are under way to determine the action and mechanism. This inhibitor Robinson (1962) commenting on these reports stated that the evidence for an endocrine functioning of the salivary glands continues to accumulate.

Feyrter (1961, 1963) investigating the possible endocrine effects of mixed tumours of the salivary glands, found that these neoplasms function in the same fashion as endocrine tumours in secreting serotonin.

In conclusion, it could be said that there appears to be considerable doubt as to any actual direct endocrine secretion of the salivary glands. However, there is little doubt that the salivary glands, their morphology, physiology and pathology are related very closely to the endocrine system, although the nature of the relationship seems to be a very complex one. Shafer and Muhler (1960) state that further work on this subject may solve some of the unexplained facts of the problem of dental caries and other oral diseases of man.

OTHER SYNDROMES RELATED TO OR SIMULATING ENDOCRINOPATHIES.

There are several conditions in this category, mainly of unknown aetiology, and which may have an endocrine connection. They will be only considered very briefly from the point of view of any possible relation or simularity to endocrine disorder.

MONGOLISM.

Mongolism is a type of mental deficiency, and is of interest because of a peculiar change in the patient's appearance, suggesting a change of race. The physical features are many and varied and include the typical almond-shaped "Mongolian-like" eyes, depressed nasal bridge, thick and broad tongue, short fingers, low pitched and raucous voice, Lisser and Escamilla (1962), Gosman (1951).

Its aetiology is claimed by Benda (1946) to be due to a congenital hypopituitarism, and a polyglandular deficiency in which all glands are at fault. The pituitary is damaged in foetal life, and the Mongoloid is born with a pituitary deficiency, which he is never able to overcome. Gosman (1951), and Brown and Cunningham (1961) also describe to this view.

However, others feel that it is due to a completely unknown cause. Conybeare and Mann (1952), state that the condition depends on non-genetic factors of whose nature we are ignorant. Lisser and Escamilla (1962), remark that it has a congenital cause involving an extra chromosome, and adds that its endocrine status remains uncertain.

Many other factors have been attributed to the aetiology also, such as advanced maternal age, and uterine and placental abnormalities, Shafer, Hine and Levy (1963), Lisser and Escamilla (1962), and maternal infection, Pleydell (1957).

The latest theory which seems to be more accepted is that of a chromosomal abberration.

Dental features of the condition have been observed and studied by Gosman (1951), Benda (1947), Dow (1951), Brown and Cunningham (1961), Pleydell (1957), Cohen et al (1961). Periodontal disease , Class III malocclusion, congenitally missing teeth, and high caries rate, hypoplasia and microdontia have all been reported.

Fig. 38

Mongolism. In boy aged 5½yrs.
Note typical facies and obvious mental deficency.
Lisser and Escamilla (1962).

Fig.39

Paget's Disease of Bone, showing considerably enlarged maxilla.
Colby, Kerr, and Robinson (1961).

Fig. 40

Gargoylism. Age 19yrs. Height 3'9½". Growth of only 9" in 14yrs. Note typical facies and enlarged abdomen. Died at age 27, due to respiratory failure from enlarging liver.

Fig.41

Gargoylism. Radiograph of skull of patient aged 5yrs. Note irregularities of vault and greatly enlarged shallow sella turcica.

Lisser and Escamilla (1962).

POLYOSTOTIC FIBROUS DYSPLASIA; albright's syndrome.

The fibrous dysplasias of bone are among the most perplexing diseases of osseous tissue there are, and not a great deal is known of their aetiology. Classification of the diseases has not been clear, but polyostotic fibrous dysplasia has recently been divided into two groups, the first involving a variable number of bones, although most of the skeleton remains normal, accompanied by pigmented lesions of the skin, and the second being more generalised and severe involving most bones of the skeleton with pigmentation of the skin and in addition endocrine disturbances of varying types, (Albright's Syndrome) Albright et al (1937 and 1938), Shafer, Hine and Levy (1963), Thoma and Goldman (1960).

The first recognised case of polyostotic fibrous dysplasia of this second type was recorded by Weil (1922). A number of similar cases have since been reported. This second type is relatively uncommon.

The chief clinical features are usually seen to commence early in life, and are an evident deformity, bowing or thickening of the long bones, which is often unilateral, spontaneous fractures, irregular pigmented spots on the skin, and precocious puberty in females. Other disturbances of the endocrine system have been reported including those of the pituitary, thyroid, parathyroid and ovary, Shafer, Hine and Levy (1963), Albright, and Reifenstein (1949).

Albright and Reifenstein (1949), remark that in their opinion the sexual precocity in females which is fairly commonly seen in the syndrome, is normally the result of the release of gonadotrophic hormone or hormones from the pituitary, which in turn is due to stimuli comming over the hypothalamic-pituitary, nervous-humoral pathway. They refer to ane woman who had her first catamenia during the first year of life and was still menstruating at the age of 54. They include female sexual precocity in a trend of dominent symptoms, together with bone changes and pigmentation.

Lichwitch (1938), believed that the cause of the condition was due to increased activity of the parathyroid hormone. At least it

seems that some endocrine disturbance is involved. Albright et al (1937, 1938), and Faulkner and Cope (1942), Caldwell and Broderick (1947), report on the endocrine signs of the disease. Mochlig and Schreiber (1940), report the case of a boy sixteen years, with gynecomastia in association with the disease. Faukner and Cope (1942), reported acromegalic features and hemianopia in the syndrome. Lichwitch (1938) reported a case of a nine year old girl with the femur affected, on one side and the patient had an ovarian cyst, hyperthyroidism, hyperglycaemia, and precocious maturity with hyperpigmentation.

In all cases reported, the blood chemistry was normal except for an occasionally seen slight rise in phosphatase. Thoma and Goldman (1960), Shafer, Hine and Levy (1963).

Lichtenstein (1938), and others have carefully described the pathology and radiography.

Oral manifestations of polyostotic fibrous dysplasia are related to the severe disturbances of the bony tissues. There may be expansion and deformity of the jaws, and disturbed eruption of the teeth because of loss of normal bone support. The endocrine disturbances may also alter the eruption times, Church (1958), Shafer, Hine and Levy (1963).

PAGET'S DISEASE, osteitis deformans.

This is a chronic bone disease of relatively common occurrence affecting usually several bones of the body, the most common being the pelvis, lumbar, spine, femur, tibia, and the skull. The skull becomes very thick and the legs become bowed, and the spine develops kyphosis causing shortening of stature.

The aetiology is still unknown despite numerous theories that have been advanced over the years, Shafer, Hine and Levy (1963), Paget originally believed the disease was an inflammatory one, and this has been supported again by some late workers. Albright and Reifenstein (1949), comment that it can be regarded as a localised bone disease as it does not affect all the bones of the body, and therefore suggests that this fact is strong evidence against any metabolic or endocrinologic aetiology. The decalcification of

hyperparathyroidism is generalised whilst the bone cysts that occur are more localised as a secondary feature of the disease. They state that Paget's Disease is not due to hyperparathyroidism, which is contrary to what had been previously suggested by a good many authors. It occurs at times together with hyperparathyroidism which is probably coincidental. However, they state that it is possible that hyperparathyroidism predisposes to Paget's Disease. They add that removal of the parathyroid glands does not cuase any dramatic improvement in a condition of Paget's Disease. Snapper (1949), also observed this. Snapper (1949), remarked that parathyroid injections assist many cases of Paget's Disease, but it does to other diseases also, so that this should not be used in favour of an endocrine aetiology. Thoma and Goldman (1960) comment that whilst some observers regard it as a varient of hyperparathyroidism, the urinalysis and blood chemistry prove that they belong to a different group. Many today believe it to be simply a bone inflammation as Paget did originally, hence the name "osteitis deformans". Another concept gaining increasing support is that a vascular abnormality is the causitive factor, Albright and Reifenstein (1949), seem to favour this. Stones (1954) states that in some cases an hereditary history has been traced. To conclude, it seems that the result of the above observations indicate the possibility of an endocrine connection.

Oral Manifestations, are an enlarged maxilla, which may be the first bone effected, Stones (1954). The bone is very vascular and soft at first, but hardens often after. The patient may complain of ill-fitting dentures due to this, which is often an early symptom. Sometimes both jaws are affected. Many authors have reported cases of this disease having oral manifestations.

LEONTIASSIS OSSIA:

This is a very rare condition which is similar to Paget's Disease, but occurs early in life whereas Paget's Disease occurs later in life. It also is a bone profilerating disease but only affects the facial bones and sometimes the skull resulting in the classial "leonine" appearance. Stones (1954), mentions that there is a good

deal of difference of opinion as to its specificity, many feeling that it is simply a variant of Paget's Disease. Drury (1962) particularly feels this, in a recent consideration of the matter, and Shafer, Hine and Levy (1963) support his views.

Very little has been said to its possible aetiology, but the remarks made on the aetiology of Paget's Disease would probably apply in this condition also.

OSTEOPETROSIS; Marble bone disease; Albers-Schonberg disease.

This is an uncommon disease, occurring usually early in life, characterised by continued deposition of bone, but impaired resorption resulting in diffuse sclerosis. The skull and jaws are affected like the other bones and can cause varied and serious symptoms. The oral manifestations of the disease were recently reviewed by Kaslick and Brustein (1962). Tooth eruption delay is a common feature.

Aetiology is unknown, but the experiments of Selye (1932), may indicate an endocrine involvement. He records that the administration of small doses of parathormone to animals over a long period produces apposition of bone with a condition similar to osteopetrosis. It should be noted that this is the opposite result to the effect of large dose intake, which causes bone resorption. Shafer, Hine and Levy, (1963), mention that osteoclasts were found in these animals (rats and mice), in normal numbers but appeared functional. This finding, they state, may be related to the fact that the osteoclasts have been shown to be deficient in ribonucleic acid. Defective genes may also be associated with the parathyroid glands in these rats. The disease is often hereditary in which case, it is transmitted as a recessive mendelian characteristic.

MYASTHENIA GRAVIS.

This is a very rare condition characterised by ready fatigability of the voluntary muscles, principally those of the eyes, lips and tongue, the essential disability being a failure of normal conduction of the motor nerve impulses at the neuro-muscular junction. The

disease begins most commonly in the first half of life and affects women more than men. Wheeler and Jack (1963).

Shafer, Hine and Levy, (1962), remark that many investigators have attempted to relate the disease to the endocrine system, suggesting an endocrine imbalance due to the occurrence of thymic hyperplasia or tumours frequently in the patient. It has also been connected with pregnancy, menstruation, and hyperthyroidism but these associations may be more apparent than real. There is no evidence of an hereditary factor being involved. Conybeare and Mann (1952), state that it occasionally coexists with exopthalmic goitre.

In addition to the oral manifestations mentioned above, there may be the difficulty in deglutition and mastication, and a dropping of the jaw, and a disturbance in the taste sensations, Stones (1954) Shafer, Hine and Levy (1963), Wheeler and Jack (1963).

ACHONDROPLASTIC DWARFISM:

This is one of the most common types of true dwarfism and is a congenital disorder, affecting endochondral bone formation. There is no apparent endocrine causation or secondary involvement.

The dwarfism is of a characteristic type, being disproportionate in the extremities. (shortness, bowed legs, lumbar lordosis, The skull and face are also characteristically involved, the upper portion being normal in size, or large and the lower relatively underdeveloped. Muscular development, sexual function, mental activity are all normal. Differentiation between this and other dwarfs is simply because of the normal sexual development. Many of these dwarfs are gymnasts in circuses and in groups of midgets. Lisser and Escamilla (1962). Shafer, Hine and Levy (1963).

GARGOYLISM; Hurlers disease, Dyostosis multiplex

This is a rare congenital disease, which may be familial, and is usually inherited as a autosomal recessive trait, characterised by a grotesque facial disfiguration resembling the gargoyles of Gothic architecture. Other characteristics are dwarfism, infantilism hepatomegaly and slenomegaly, thick skin, poorly developed maxilla,

and ascending ramus, resulting in mandibular protrusion, retarded epiphyseal closure etc. Lisser and Escamilla (1962).

Cawson (1962), in an interesting article considers the oral changes in Gargoylism.

LAURENCE -MOON-BIEDL. SYNDROME.

This is a rare syndrome in which a hypogonadism is sometimes found. Hypopituitarism has been suggested as a cause but this is dubious. Its main features are an adiposogenital-type obesity, skeletal abnormalities, a typical retinitis pigmentosa, mental deficiency, and a familial occurrence.

MARFAN'S SYNDROME.

This is a rare congenital hereditary condition involving ocular, skeletal and cardiovascular abnormalities. A high palatal vault is common found, giving the patient a high-pitched voice. Fitch and Secord (1963) described the oral manifestations.

MOROUIRO'S DISEASE.

This is a rare disease of the bones somewhat like achondroplasia but deformities are more pronounced in the spine and thorax. Enlarged head and flattened nose is common.

MAFFUCCI'S SYNDROME.

This rare syndrome involves a dyschondroplasia with multiple haemangiomas. These haemangiomas are apparent in the skin and mucous membranes.

CONRADI'S DISEASE

This rare disease is characterised by stippled calcified foci in the hyaline cartilages of the epiphyses and apophyses. Dwarfism of the short-limbed type occurs in about half of the cases. A flattened bridge of the nose, high palate, and dry scaly skin area also associated with the syndrome.

HYPEROSTOSOS FRONTALIS INTERNA;

Thickened inner tables of the frontal and occasionally the parietal bones, and sometimes other parts of the skull are found in this rare condition. Metabolic irregularities are not consistantly found but do occur in some cases; s'ich as pituitary and adrenal involvements manifesting themselves in obesity, hirsuitism, diabetes mellitus and insipidis, hypercalcaemia, hypertension, menstrual disturbances, and a general altered thyroid and pituitary function. However, most feel that an endocrine aetiology is dubious.

ENDOCRINE THERAPY IN DENTAL SURGERY.

This is primarily restricted to the local use of endocrine preparations. The employment of endocrine therapy in dentistry per se is not justified. There is no evidence that alterations in endocrine function give rise to oral or dental symptoms without producing other systemic symptoms. When systemic manifestations are present, the responsibility for endocrine therapy rests with the physician, Schour and Massler (1943).

It must be kept in mind that nutritional and hereditary factors are as equally important as endocrine factors, in the matter of systemic disease, affecting the oral region. Failure to recognise this in the past resulted in clinicians tending at times to yield to the temptation to invoke the endocrine when confronted with a puzzling clinical problem. This lead to many incorrect theories, connecting endocrine disorders with caries, orthodontic problems and periodontal conditions. For the most part the statements in the literature (which are numerous in past years) that relate endocrine dysfunction aetiologically to dental disease are not supported by clinical or experimental evidence, and represent at best "a hunch" in the part of the particular investigator. Schour and Massler (1943)

The dentist has the opportunity of recognising in his patients oral manifestations of possible endocrine dysfunction (periodontal conditions, orthodontic conditions and craniofacial abnormalities, and the responsibility for referring them to a physician for diagnosis confirmation and treatment if indicated. Schour and Massler (1943).

A warning must be included here as to the danger of steroid therapy particularly. The secondary effects of a hormone may be more undesirable than the apparent ameliorative action it affords. This is becoming increasingly obvious, especially with cortisone therapy. Also the sex hormones have the constant possibility when given therapeutically of carcinogenic effects. Speert (1948), Engel (1952), Blackburn (1955).

Gingivitis and Stomatitis.

Speert (1948), indicates that the steroids and synthetic hormones can be absorbed by the oral mucosa in functional quantities. There substances are used because of their antiinflammatory effects.

Glickman (1958), gives the dosages and methods of administration of hormones for gingival conditions.

Hydrocortisone acetate ointment applied to the gingivae in the treatment of inflammatory gingivitis, desquammative gingivitis, glossodynnia, cheilitis, leukoplakia, denture-sore mouths, drug allergies affecting oral mucosa lesions, and burns has been reported successfully, Fisher (1955), Strean and Horton (1953), Thoma (1963) etc,

Bain (1954), successfully treated pregnancy gingivitis with cortisone.

Staple (1953), suggests that the gingival hyperplasia seen in patients given sodium dilantin may be the result of adrenocortical dysfunction as a result of some work done on ferrets. Strean and Horton (1953), reported that the hyperplasia of dilantin gingivitis did not return after surgery, as long as hydrocortisone ointment was applied twice a day for three months. However, Sackler et al (1954), could not produce these results.

Injections of cortisone and hydrocortisone into the oral mucosa has been used, and suggested by several authors (Iusem, 1956, etc), in the treatment of hypertrophic gingivitis but both Fox and Stahl, (1955), and Messina (1958), who investigated the matter fully, found that there was little or no permanent effects.

However, it must be kept in mind that Ziskin (1938), and Ziskin et al (1936), found that some gonadotrophins apparently cause undesirable gingival changes.

Cases of glossodynia and cheilitis were successfully treated with hydrocortisone ointment by Fisher (1955), He also treated stomatitis due to irrating dentures, and allergy, by the same method. Allergy stomatitis has also been successfully treated with ACTH and cortisone. Dreizen et al (1952).

Systemic administration of steroids has proved useful in causing a subsiding of oral manifestations of angioneurotic oedema, drug sensitivity, pemphigus, periarteritis nodosa, acute leukaemia, idiopathic thrombocytopenic purpura, etc. but is the physician's responsibility, Strean and Horton (1953). Weisberger (1960) alludes also to some of these systemic diseases, and suggests dosages for treatment of pemphigus, erythema multiforme, and lichen planus. For the latter two mentioned he suggests giving one 5mg tablet three times daily of prednisone (Metacortin) for four days, reducing it then gradually down to half a tablet daily by the tenth day.

Desquamative Gingivitis.

Corticosteroids have been used successfully in the form of hydrocortisone acetate ointment, and to a lesser extent by local injection, in the treatment of this condition when all other attempts to alleviate it were unsuccessful. Strean (1950), Strean and Horton (1953). On the other hand others state that even this form of treatment is only useful in some cases, McCarthy et al (1960), Thoma and Goldman (1960), Weisberger (1960), Robinson (1962).

Oestrogens have also been used with a measure of success in the form of oestradiol benzoate ointment, Ziskin (1937). Others refer to this line of treatment, and mention at the same time the need for care in view of the possible side effects, Van Minden (1946), Speert (1948), Trott (1957), Glickman (1958). Injection of oestradiol dipropionate into the mucobuccal fold has also been used to successfully alleviate the dry and burning sensation of the gingivae, and increase salivation, in this condition, Rickman and Abbanbanel (1943). Massler (1951), Lisser and Escamilla (1962), and others remark that oestrogens should only be given in severe cases.

Androgens (testosterone) have also been used with a measure of success, but side effects have to be watched (virilisation), Massler (1951), Glickman (1958). Weisberger (1960) comments that the sex hormones have not been proven to be of much value in the treatment of these conditions.

For further details on the treatment of Chronic desquamative gingivitis see p. 235-236.

Aphthous Ulceration;

When this occurs on the lips or oral mucosa, the use of cortisone or hydrocortisone has been beneficial. Strean and Horton (1953), advocate the use of hydrocortisone ointment, topically applied. This was further investigated by Bergmen (1954), on seventeen patients, fifteen of which showed prompt improvement, when most other therapeutic agents failed. He used both a one, and a two and a half percent concentration of hydrocortisone acetate, the former being satisfactory for all but severe cases.

More recently hydrocortisone acetate tablets has been widely used, the method being to allow the tablet to slowly dissolve on the ulcer. Fairly satisfactory and consistant results have been achieved by using this method. A reduction in the discomfort and the period of ulceration occurs. Thoma (1963) refers to the use of a combination drug called "Hydrozets", consisting of hydrocortisone acetate, an antibiotic and topical anaesthetic, in the form of a troche, which has been reported successful.

Some writers however are apprehensive as to the efficacy of these drugs in aphthous ulceration. Accepted dental Remedies (1962) does not recommend them at all. Weisberger (1960) comments that the steroids are useful only to some extent in recurrent aphthous stomatitis.

Root Canal Therapy.

Root canals, in root canal therapy, saturated after sterilisation with a hydrocortisone saline suspension, lead to reduction of inflammation and pain in the periapical region, according to the reports of Wolfsohn (1954), and Strean and Horton (1953).

This periapical inflammation is often due to to procedure of pulpectomy and cleansing of the root canal. Hydrocortisone was found to reduce this in the ten cases examined by Strean and Horton (1953) and in the survey of Wolfsohn (1954).

Another method has been used whereby hydrocortisone acetate saline suspension was injected intraosseously and supraosseously in the periapical area, Strean and Horton (1953).

It must bee concluded that the results of these techniqu not been sufficently good enough and consistent to warrant from other ones.

Pulp Capping and Pulpotomy.

Hydrocortisone acetate suspension has been used as a pulp capping agent in sixty cases of vital exposure of the pulp and vital pulpetomy, by Rapoport and Abramson (1958). They stated that there was a high degree of success reached, but emphasised that it could only be regarded as a preliminary report, because of no controls being used.

A more extensive investigation was made by Fiore-Donno and Baume (1962, 1963), who studied 190 teeth which had pulpitis and were pulp capped with four different capping compounds, all containing a corticosteroid and chloramphenicol and other substances. Whilst apparently good clinical results occurred immediately after treatment, the histologic examination on some of the teeth, which had to be subsequently extracted because of prosthetic or other reasons, revealed absence of a solid barrier of dentine underneath and evidences of chronic inflammation of the pulp. These tests were carefully carried o out with controls. The compound containing prednisolone had the worst effect and that containing dexamethasone-methylcellulose-chloramphenicol had the least effect.

It can be safely concluded from these results that corticosteroids in pulp capping and pulpotomy techniques is of questionable benefit.

Alveolar bone.

Becks et al (1944), reported that ACTH inhibits bone growth in rats, and Applebaum and Seelig (1955), reported a loss of septal bone after three months of daily injections of cortisone to rats. Goldsmith (1953), said that rats on a long term period of cortisone therapy (one year), showed an increase in the amount of bone and narrowing of the marrow space, in the alveolus. Glickman and Shklar (1954), observed osteoporotic changes in the alveolar bone on cortisone treated mice. However Douglas and Kresberg (1956), pointed out that Glickman in his experiments administered a dose twenty times greater than would be administered in humans. Kerr (1955), also indicated the danger in applying the results in experiments on animals as being valid for human beings.

Temporomandibular Joint;

Spies et al (1952), and Strean (1952), presented encouraging results with cortisone (Kendall's Compound E) used systemically in the treatment of arthritis of the temporomaddibular joint. Hollander et al (1952), used both cortisone and hydrocortisone injected into arthritio joints with good results. Remissions of signs and symptoms was observed in over 98 percent of various arthritic joints, treated by intracticular injection of hydrocortison

Strean and Horton (1953) reported five cases where the temporo-mandibular joint was injected with hydrocortisone acetate saline suspension, with good results, and gives the method of injection. They found it successful in cases where the joint was affected by rheumatoid arthritis, osteoarthritis, and trauma. In advances cases of arthritic temporomandibular joints one injection was usually not found sufficent, and repeated injections were often necessary.

Thoma (1963) mentions several corticosteroid drugs useful in the treatment of temporomandibular arthritis, (Sigmagen, Medrol, Decadron Butazolidin).

Many investigators have proved that this method of treatment is of definite benefit in the easing of the unpleasant symptoms of these conditions.

Oral Surgery.

Hydrocortisone acetate ointment has been suggested for use under immediate dentures with varying results, Amesbury (1956) etc. Howeven corticosteroids applied in this way to such inflamed sites, whilst they may relieve distressing symptoms, on the other hand may interfere with the natural defence processes affecting the cause, Accepted Dental Remedies, (1962).

Premarin (a conjugated oestrogen preparation) has been reported to be useful in the arrest or diminishing of profuse oozing from operation sites, as well as in spontaneous bleeding or secondary haemorrhage after operations. The drug seems to have a direct effect on the vascular integrity of the capillaries and may have a

beneficial effect on the clotting mechanisms of the body, speeding it or supplying some missing factor. Jacobson (1955). Later Johnson and Seegers (1957), and Johnsen (1957), demonstrated that it has a very great effect on blood coagulation. It increases the concentration of prothrombin and AC globulin and decreases the concentration of antithrombin of plasma, thereby promoting normal coagulation. It is an outstanding therapeutic emergency, and it has the advantage that it can be administered with impunity, having no toxic effects and no oestrogenic side-effects if administered in short periods, Thoma (1963). Menger (1955), found it very useful in stopping epistaxis and haemorrhage after adenoidectomy. Roberts, (1961), recommends its use with patients on a long term anticoagulant therapy, who have to undergo surgical procedures such as dental extractions. Nathanson (1958), reports that its use routinely in oral surgery eliminates the problem of excessive bleeding. Thoma (1963), has used it successfully where excessive capillary oozing, or bone haemorrhage is encountered.

CONCLUDING SUMMARY OF THE ORAL MANIFESTATIONS OF ENDOCRINOPATHY

SYNDROME	CRANIO-FACIAL FEATURES	THE JAWS	THE TEETH	ALVEOLAR BONE	THE ORAL MUCOSA PERIODONT.	SALIVARY GLANDS
PITUITARY GIGANTISM	+ Growth	+ Growth	+ teeth + eruption			
EUNUNCHOID GIGANTISM	+ Growth	+ Growth	anodontia of laterals			
ACROMEGALY	Prognathism Thick lips + Nose Thick skin	Mandib. protrusion Obtuse angle Jaw pain	Spacing of lower teeth		Enlarged tongue	
Experimental HYPERPITUIT.	+ Growth	Acromegaloid features	+ size teeth	Denser bone		
Hypophyseal INFANTILISM	- Growth - face	Maxillary protrusion - Jaws	- eruption & shedding - roots			
SIMMOND'S DISEASE	Cachexia - hair		+ Caries. + Loss of			
PITUITARY MYXEDEMA	Myxedematous face.		+ Caries + loss of			
EXPERIMENTAL HYPOPITUITAR. Hypophysectomy	- Growth	Advanced condylar ossification	-growth -eruption -size apical folding - roots - calcif.		Chronic periodontitis	changes in structure
FROHLICH'S SYNDROME	Obesity of face. Smoothe skin - hair		+ eruption Poorly formed			
PROGERIA	-face - hair inelastic skin	Micrognathia High pal. arch	crowded - eruption less teeth	Poorly calcified		
DIABETES INSIPIDIS			+ Caries		Gingivitis	-Secret.
PINEAL TUMOURS	Precocious developm't.	+Growth	+Growth + eruption			
THYROTOXICOSIS Graves Disease	Exopthal mos. protruding bones		+ eruption - calcif.	osteoporosis periapical bone loss	sepsis periodontitis ?	

SYNDROME	CRANIO-FACIAL FEATURES	THE JAWS	THE TEETH	ALVEOLAR BONE	THE ORAL MUCOSA PERIODONTM.	SALIVARY GLANDS
EXPERIMENTAL HYPERTHYROIDISM	loss of)HAIR	+	+eruption -Ca olific. -dentine	osteoporosis loosening of the teeth	smoothe red tongue	changed structure +secretion -viscosity
CRETINISM	-growth	micrognathia malocclusion	-growth -eruption +caries		enlarged tongue	
CHILDHOOD MYXEDEMA	wide, short face	micrognathia malocclus.	absent?? hypoplasia			
ADULT MYXEDEMA			+caries		chronic periodontitis	
EXPERIMENTAL HYPOTHYROIDISM	-growth	micrognathia delayed osteogenesis	-growth -eruption -Calcif. hypoplasia +caries	-new bone apposition	keratosis oedema	-secretn. +viscosty -tubules of gland
THYROIDITIS		pain in jaws			pharyngitis painful deglutition	
OSTEITIS FIB. GENERALISATA	giant cell tumours of forehead and jaws	decalcified mottling g.c. tumours malocclusion	spacing due to tumours -caries	osteoporosis miliary mottling	loss of lamina dure	+secretion
EXPERIMENTAL HYPERPARATHYR	"	"	calcio-traum line in dentine	osteoporosis loosening	of teeth	
PARATHYROID TETANY		open bite in children	hypoplasia in childn. or aplasia -eruption -roots -calcif. +caries?	densor bone		
PSEUDOHYPO-PARATHYROID.			)-eruption -- roots	abnormal bone		
EXPERIMENTAL HYPOPARATHYR.			-dentine -calcif. hypoplasia aplasia pulpal defects			salivary calcium increased

SYNDROME	CRANIO-FACIAL FEATURES	THE JAWS	THE TEETH	ALVEOLAR BONE	THE ORAL MUCOSA PERIODONTM	SALIVARY GLANDS
EXPERIMENTAL HYPERTHYMISM	+ Growth		+ eruption and growth?			
EXPERIMENTAL HYPOTHYMISM	-Growth?		-eruption?			
HYPERINSULINISM	Numbness of lips				Numbness associated with mouth	
DIABETES MELLITUS			caries?	Osteoporosis Alveolar resprption	Diabetic stomatitis Dry mouth Periodont. widening periodontitis glossitis	
CUSHING'S SYNDROME	obesity of face hirsutism exopthalmos?		osteoporosis	and loss of lamina dura	Delayed wound healing	
ADRENOGENITAL SYNDROME	+ growth but final dwarfism + sex features	+ growth	+ eruption + growth			
PRIMARY ALDOSTERONISM	parasthesia of face				dry mouth beefy red tongue	
EXPERIMENTAL HYPERADRENOCORT.		cleft pal in offspring	OSTEOPOROSIS	of alv. bone	gingivosis? - healing	+ secretr
ACUTE HYPOADRENOCORT.	fulminating purpura petechae of face					
ADDISON'S DISEASE	pigmentation of lips and face		+ caries?		pigmentation of oral mucosa	
EXPERIMENTAL HYPOADRENOCORT.			+ caries			changes structure
HYPERADRENALISM	PALLOR				pallor of mucosa	

SYNDROME	CRANIO-FACIAL PELATIRES	THE JAWS	THE TEETH	ALVEOLAR BONE	THE ORAL MUCOSA PERIODONTM.	SALIVARY GLANDS
HYPERGONADISM Precocious puh.	+ growth . final dwarfism.	+ growth of maxilla	+eruption + growth spacing			
EXPERIMENTAL HYPERGONADISM	+ growth final dwarfism	New bone apposition increased	+ caries	+new bone	hyperkerat- hiasation downgrowth epithel.att.	+ changes in the tubules
EUNUCHOIDISM AND EUNUCHISM	childish facies but large wide head	+ growth	small or absent 21 2 - calcif. + caries			
GONADAL DYSGENESIS	-growth facial moles			osteoporosis		
MALE PSEUDO-HERMAPHRODITISM	feminine facies	narrowx mandible high palate	crowded lower teeth			
PUBERTY		malocclusion		osteoporosis	Pubertal gingivitis	
MENSTRUATION	Herpes labialis Cheilitis		hyperaemia of pulp		Stomatitis dysmenorrhoea aphthous ulceration	+ size
PREGNANCY	pigmentation of skin		+ caries	osteoporosis	Gingivitis gravidarum Pregnancy tumours	+saliv. + acid
LACTATION			+ caries		subsiding of gingivitis	
MENOPAUSE CLIMACTERIUM	Skin atrophy - elestic			osteoporosis	Gingivosis atrophic glossitis Herpes ulcers	
EXPERIMENTAL HYPOGONADISM	+ growth		- eruption - calcif. - caries	osteoporosis		changes in the tubukes - proteas

+ means increased or accelerated
- means decreased or retarded.