B. HEREDITARY BENIGN INTRAEPITHELIAL DYSKERATOSIS.

Introduction:

Many of the descendants of a Caucasian woman, born in 1834, who are now members of a tri-racial (Caucasian, American Indian and Negroid) isolate residing in Halifax County, North Carolina, demonstrate a syndrome of eye lesions involving the conjunctiva, invariably associated with soft, white lesions of the oral mucosa. Nothing is known about the ancestry of the original white woman involved, as far as pathology is concerned. The condition was reported first in 1954, since which time it has been studied and described by Witkop et al (1960). Five hundred and forty (540) persons were examined in all, including 345 of the 582 living descendants of the aforementioned woman. One hundred and ninety five (195) other people of the community were also examined. Seventy five (75) of the descendants were affected, while none of the 195 unrelated control group demonstrated any similar lesions whatsoever. Affected persons were also found among more distant descendants in an adjacent county.

Clinical Features:

The oral lesions appear generally as white, spongy, macerated areas which are with or without folds, involving the buccal and labial mucosae, the floor of the mouth, lateral border of the tongue, a distribution consistent with, among others, white sponge nevus or even the keratoses which diseases it resembles in appearance. Some mouths show lesions which are very thick & widespread, others much less so, with an opalescent white membrane. Witkop et al (1960) noticed that

if the mucosa were scraped to remove the superficial cells, then stretched, the surface appeared to be covered with pin-point elevations that looked like opaque plastic points. The lesions involving the corners of the mouth were soft plaques covered with fine lines dividing the surface into rectangles, and resembled the dermal pattern on elephant hide. The most consistent clinical findings in all stages were these pin-point elevations appearing when the mucosa was stretched, and the plaques at the corners of the mouth.

The eye lesion is a foamy, jelly-like plaque on a hyperaemic background (called "red eye", locally) and the sufferer usually exhibits photophobia. Permanent blindness can result from the condition. Interestingly, these eye lesions mostly have a seasonal variation, tending to appear or increase in severity in the Spring, and disappear sometimes by spontaneous shedding of the pseudomembrane by Autumn.

Vaginal, rectal, nasal and ear examinations revealed no similar involvement.

Diagnosis and Histopathology:

The histological findings in the oral and conjunctival mucosal lesions were similar, consisting of hyperplasia of the epithelium, acanthosis, vacuolation of the prickle cells and intra-epithelial dyskeratosis characterised by waxy eosinopholic cells and a "cell within cell" pattern.

The three criteria for a positive diagnosis consist of the overall maturation pattern of a slide determined by the method of Witkop, the presence of numerous eosinophilic or so-called "tobacco" cells and the

"cell within cell" arrangement, which probably represents atypical epithelial pearls.

In examining a normal buccal mucosa with the Papanicolaou stain, the typical maturation pattern of the cells shows blue - and red-staining cells in the proportion of two to three, with an occasional yellow cell. The blue cells are mostly "inner layer" squamous cells and the red are "outer layer" squamous cells, which roughly correspond to the precornified and cornified cells of mucous membrane.

In contrast to the above normal patterns, the scrapings from affected persons showed a cytoplasmic maturation pattern characterised by a predominance of red/orange staining cells in the ratio of about 77:23. A great part of the orange maturation pattern was ascribed to the presence of numerous "tobacco cells", so named because their colour resembled the amber-brown-orange of tobacco particles sometimes seen in Papanicolaou stained oral smears. These latter cells vary in size from about 7μ x 11μ to 28μ x 22μ, have a waxy-looking cytoplasm usually free of folds, in contrast to the usual wrinkled orange variant of red outer squamous cells in patients with parakeratosis.

The "cell within cell" appearance is seen as an internal body, seemingly a "tobacco cell" surrounded by a more normal-looking pre-cornified or cornified cell. The nucleus of the normal cell appears pushed to one side, assuming a half-moon or sickle shape. The dyskeratotic or centre cell is surrounded by a very refractile non-staining membrane.

The condition can be diagnosed easily by the Papanicolaou method, through which "tobacco cells" and "cell within cell" pattern are demonstrated. An occasional epithelial pearl may be found in other conditions, but not with the frequency and staining qualities seen in benign dyskeratosis. Trott (1956), however, reported eosinophilic dyskeratotic cells in white sponge nevus.

Differential Diagnosis:

It is felt that any differentiation should not be solely clinical, although the concurrent eye lesions would almost decide the issue.

In contrast to white sponge nevus, which benign dyskeratosis so resembles, no patient had vaginal or anal lesions. Further, none of the recently published cases of white sponge nevus has shown eye lesions.

There are histological differences, in that hereditary benign intraepithelial dyskeratosis possesses eosinophilic dyskeratotic cells and "cell within cell" dyskeratosis, usually not found in white sponge nevus, while otherwise histologically they are similar.

Witkop et al reported one patient, not related to their isolate group, with a condition diagnosed as white sponge nevus, who had typical oral, anal and nasal lesions which showed an eosinophilic "cell within cell" dyskeratosis in a biopsy taken in 1954, but which dyskeratosis was not present in repeated biopsies in 1959.

The disease could be a variant of white sponge nevus, "but the several differences suggest a new hereditary disease." (Witkop et al). Hereditary benign intraepithelial dyskeratosis seems completely benign: no neoplastic disease or change has been noticed in the lesions.

It is inherited, it seems, as an autosomal dominant trait with high degree of penetrance.

Treatment is not indicated.

C. PACHYONYCHIA CONGENITA.

This is a rare disease, congenital in origin; sometimes, but not always, familial (Shafer et al) and was originally described by Jadassohn and Lewandowski in 1906.

Clinical:

The disease is characterised by dystrophic changes in the finger-nails and toe nails, hyperkeratoses or callosities of the palms and soles, follicular acneiform keratosis particularly about the knees and elbows and hyperhidrosis or excess sweating of the hands and feet. Dystrophic changes of the cornea and hair are occasionally observed. Verrucous lesions may appear on the elbows, but they are especially common on the lower extremities between the knees and the ankles. Plantar bullae are not common. Oral lesions are nearly always present (Gorlin and Chaudhry, 1958). They take the form of white, opaque, plaque-like lesions, either focal or quite generalised, even covering the entire mucosa of the tongue, lip and cheek. Angular cheilosis, with white lesion involvement, is common. The nail lesions appear usually at birth or soon afterwards. Skin lesions can be present at birth, but often appear when the child is 18 months to 2 years of age. Oral lesions have been noted at birth, but several other reports did not specify the age at which they appeared (Gorlin and Chaudhry).

McCarthy and Shklar (1964) felt that, even though there is a variety of associated anomalies described, the outstanding triad in diagnosis is leukoplakic lesions of the oral mucosa, palmar and plantar hyperkeratosis and peculiar dystrophic changes in the nails.

Occurrence:

So far, there have been very few cases of pachyonychia congenita reported.

In the analysis of some reports, it seems there could have been some confusion, owing to the variety of applied names, such as "Hyperkeratosis of the Oral Mucous Membrane, associated with hyperkeratosis palmo-plantaris hereditaria" - (Hiatt and Orban, 1960) - "Dyskeratosis Congenita" - (Costello and Buncke, 1956) - "Dyskeratosis Congenita with pigmentation, Dystrophia Unguis and Leukokeratosis Oris", the latter term used by Cole Snr. et al in 1930. This last named condition closely resembled the original pachyonychia congenita of Jadassohn and Lewandowski, and in the writer's opinion, seemed to be another manifestation of the same disease, i.e. Pachyonychia Congenita. But in an article written by Costello and Buncke, Cole Jnr. stated in a discussion on the Cole Snr. et al disease, "that because of the dystrophic changes in the nails in association with marked leucoplakia of the tongue and buccal mucosa, it was felt that it deserved a place as a distinct entity." The "entity" seems to the author to be pachyonychia congenita.

Till 1956, stated Costello and Buncke, only one (1) case of the condition had been reported in Europe. They, at the time, were reporting a second case, but, under the name of "dyskeratosis congenita"

as they described it, other cases may previously have been missed.

In a report of a case of pachyonychia congenita by Buckley and Cassuto (1962), as well as the usual areas of involvement, there were bilateral corneal eye lesions, rust coloured and in an unusual configuration. Could this have any relation to Witkop's " Hereditary Benign Intraepithelial Dyskeratosis?".

Gorlin and Chaudhry (1958) reported that males have been more affected than females in the proportion of 2:1, but it seems that the number of cases so far reported is too small to dogmatise. Costello and Buncke asserted that the disease had only been reported in males, but this could be probably due to confusion in disease name, although Gorlin and Chaudhry did write their article about 2 years after Costello and Buncke, thus having been given more time for further reports, if any, to be published.

Jackson and Lawler, as reported by McCarthy and Shklar, suggested that the disease is transmitted as a dominant character, but seldom continued for more than two generations. This is borne out by one instance reported by Hiatt and Orban (1960) of a grandmother, aged 76 and her son, aged 40 years, who were both affected by pachyonychia congenita, while the grandchild, or son's son, was not.

In a case seen by McCarthy and Shklar, no other member of the family showed similar involvement.

Histology:

The mucous membrane exhibits acanthosis and intra-cellular oedema or vacuolation of the spinous cells. Parakeratosis or hyerkeratosis is usually evident. No features are pathognomonic (Shafer et al, 1963).

However, Hiatt and Orban, reporting on biopsies of various areas of the oral cavity in a male aged 40 years with pachyonychia congenita, found some striking features. The epithelium was thickened and the rete pegs elongated and widened. The tips of the pegs were also rounded and sharply separated from the connective tissue. The basal cell layer was regular and intact, but mitotic activity was increased. Hyperkeratosis and some parakeratosis were present. The granular layer was unusual, in that, instead of the normal composition of flat cells with granular cytoplasm, there were no flattened epithelial cells: on the contrary, the granular layer cells were rather irregular and lightly staining with disseminated granules, and were still of usual "bulk". In some areas, the granules extended into the body of the epithelial ridges.

The most characteristic feature was the presence of large masses of eosinophilic granules, which were found next to the dark blue kerato-hyaline granules. Many of the cell nuclei were pyknotic. Whereas the kerato-hyaline granules stopped at the border between prickle cell and granular layers, the eosinophilic granular mass extended deep into the epithelial ridges in many areas. These eosinophilic granules seemed to lie in degenerated cytoplasm of the cells and also seemed present in intercellular spaces. Intercellular bridges were mostly present, as is normal in the malpighian layer.

Very little inflammation was observed in the corium; just a few lymphocytes in places.

This case caused Hiatt and Orban some concern as to whether it could be a "simplex" hyperkeratosis or even a "complex" condition.

However, they decided to observe the patient at regular intervals, repeating biopsies.

Therapy:

There is no treatment indicated usually, as the disease is not considered serious. However, if Hiatt and Orban's case were to prove pre-cancerous, all white lesions of the oral involvement in their patient should be removed. All irritation should be eliminated in these cases, in order to prevent aggravation of the lesions. Perhaps local application of Vitamin A would help to counteract the tendency to disturbance in the maturation process of the epithelial cells.

D. INHERITED KERATOTIC LESIONS (Unnamed).

There seem to be some features common to all the dyskeratoses congenita. Other dyskeratoses than pachyonychia congenita exhibit manifestations in different sites: there may be features present in some and absent in others. McCarthy and Shklar reported having seen hereditary keratotic white lesions of the oral cavity that do not fit into any named dyskeratotic or hyperkeratotic syndrome. This is not difficult to understand, in view of the diversity of possible sites of involvement and it does not follow that dystrophic changes should affect certain parts only or even be identical in appearance.

Cases reported have not, to the author's mind, shown evidence of dominant inheritance, but rather evidence of a recessive type.

SECTION 7.

MISCELLANEOUS CONDITIONS PRODUCING ORAL WHITE LESIONS.

A. MONILIASIS (Thrush)

B. GEOTRICHOSIS

C. SYPHILIS

D. FORDYCE'S DISEASE

E. BOHN'S NODULES

F. (WHITE) HAIRY TONGUE

G. GEOGRAPHIC TONGUE

H. ATROPHIC SENILE GINGIVITIS (and comparison with Chronic Desquamative Gingivitis).

MISCELLANEOUS CONDITIONS PRODUCING ORAL WHITE LESIONS.

A. MONILIASIS (Candidiasis) or Thrush.

1. Introduction.

The first description of Thrush, said Wagner et al (1959) is by Rosen von Rosenstein, who, in 1764, spoke of a disease of the mouth which could spread to the lungs and other parts of the body.

Moniliasis is a fungus infection caused by a yeast-like organism, Monilia (Candida) albicans, which fungus is often a normal inhabitant of the oral cavity and gastro-intestinal tract of unaffected persons, occurring, indeed, on most mucous membrane surfaces. There must be actual penetration of the tissues in order to produce the disease, so that isolation of this organism from a diseased mucous membrane of itself means little or nothing, since it grows readily on many pre-existing pathologic processes; McCarthy and Shklar (1964) stated that thrush is often diagnosed incorrectly, a condition being named "Thrush",when strictly it is not.

The disease may affect the oral cavity, the gastro-intestinal tract, the urinary tract, the genitals, the lungs and/or the skin. Lesions of the mucous membranes are called "Thrush", particularly those of the mucous membrane of the mouth. Infections have also been reported of the nails, lymph nodes, the spleen, the liver and the meninges.

Oral thrush, which itself can be a severe disease when lesions are extensive enough or in such sites as to interfere with eating, may

spread due to lack of resistance brought on by malnutrition, thus affecting the system in general and setting up a vicious circle (Wagner et al, 1959).

Perlèche (French, "pour lècher", to lick) is a clinical description of a fissuring and folding at the corners of the mouth, in which fissures and folds, candidiasis may develop.

Finnerud (1944) defined the different aetiological or predisposing conditions in the production of Perlèche, such as overclosure of the bite, riboflavin deficiency or pachyonychia congenita (q.v.).

In the author's view, perlèche is not angular thrush per se, but thrush may be superimposed on an already existing condition of perlèche.

2. Candida albicans.

Conant (1948) defined Candida albicans as an oval, budding, yeast-like fungus, producing both blastospores and pseudomycelia in tissues and exudates and in cultures at room temperature or at 37°C. In fresh preparations, C. albicans is a fungus 2.5 x 4 to 6µ in size, with occasional hyphal fragments 2.5 x 6 to 12µ. It is Gram positive.

Sabouraud's glucose agar was used by Conant as the culture medium, cultures becoming apparent in 4 to 5 days at room temperature, or in one (1) to two (2) days at 37°C. Colonies of Candida albicans are enamel white and have a peculiar "beery" odour because of the fermentation of sugars (McCarthy and Shklar, 1964). It is different from the true yeasts because of the production of these hyphal fragments in addition to the usual budding cells. Characteristic chlamydospores are produced on corn-meal agar.

It is a diagnostic test of C. albicans that intravenous injection of a suspension of the fungus in a rabbit, kills the animal in four (4) days, producing multiple abscesses in the kidney.

In an article on salivary yeast population and the identification of C. albicans, using the Pagano-Levin medium as a presumptive identification of strains of Candida, Bartels and Bleckman (1962) made a survey of 320 saliva specimens from 160 individuals, aged between 20 and 30 years, one half stimulated by paraffin chewing and the other half unstimulated: of the 320 specimens, 40 per cent contained yeasts, of which 75.8 per cent were species Candida; and, of this latter percentage, 60 per cent were C. albicans.

Conant stated that Candida can be cultured from the normal mouth, intestine and vagina in 35-40 per cent of the population and about 20 per cent of this number is C. albicans.

It is seen, therefore, that younger people, aged 20 to 30 years, have a higher proportion of C. albicans in the mouth, as compared with the general population. Lilienthal (1955) gave a figure of 33 per cent for the normal and constant presence of C. albicans in the mouths of young adults who have no clinical signs of Thrush; a higher figure even than the one of Bartels and Bleckman. In infants, the mere presence of C. albicans, he stated, in the mouth is usually associated with Thrush.

From these two findings, two questions immediately presented themselves:-

(1) Do the strains found in infants differ in infectivity from those found in young adults?

and (2) does the resistance of the tissues increase with age?

He had also noted the present, at that time, increase in generalised infections of candidiasis, where previously they were rare. Therefore, he concerned himself with the pathogenicity of oral strains of C. albicans isolated from the mouths of patients with thrush and also those with normal mouths, in order to answer question (1). The results suggested that the pathogenicity of C. albicans varies considerably and that the property of pathogenicity is unrelated to the ability to produce infection under similar conditions, as tests failed to show any signs of a difference between the strains from normal mouths and those from thrush mouths.

Conant agreed with the general concensus of opinion, stated in a previous paragraph, that the exact aetiologic significance of C. albicans in any disease process is difficult to establish, since it is so frequently found in the normal mouth and intestinal tract, or as a secondary contaminant of other recognised diseases.

Kourilsky (1960) also agreed with the above statement, saying too, that Candidiasis may be produced as just another manifestation of an idiopathic allergy. Candida albicans is considered the sole pathogenic member of the genus Candida.

3. Predisposing Factors (to the disease process)

It seems to the author that a predisposing factor is involved in the "triggering" of moniliasis, although this can possibly be said for any infection, except that, in the case of moniliasis, the predisposing factors seem more obvious, such as in the classic example

of a pneumonia, caused by pneumococcus, but predisposed by alcoholism.

The three main predisposing factors are coupled with infancy, old age and debilitation, where infancy and old age can be said to be "times" of lack of resistance and, therefore, "predisposing".

Tissue resistance, too, is tied up with predisposition and investigation of tissue resistance could throw light on the question asked by Lilienthal, in 1955, as mentioned in the previous section.

The use of broad spectrum antibiotics seems to play a part in the production of moniliasis, but McCarthy and Shklar stated that "true moniliasis of the mucous membrane is an uncommon complication of antibiotic therapy".

In 1947, Zimmerman et al. stated that one case of thrush they treated by the use of streptomycin therapy was cured, despite meningeal complications. In this case, the mouth, palate, tongue and pharynx were affected with large, white patches. Whether the causative agent of the meningeal condition was C. albicans is not stated or whether the meningitis was definitely apparent before the advent of moniliasis and vice-versa.

Similarly, Trott (1956) found a case of "Classical Moniliasis" in a healthy young adult male, the reason for its appearance only being explained by the concomitant presence of a Vincent's infection brought about by erupting 3rd molars, or the fact that antibiotics over a period of 18 months previously had been used. Local penicillin was used against the concurrent Vincent's condition and yet the moniliasis did not spread; rather there was a disappearance of the clinical signs of moniliasis without specific treatment: this suggests

that the predisposing factor was the Vincent's infection - when it was cured, the moniliasis disappeared. Therefore tissue resistance and/or bacterial flora balance seems to play a definite role in the aetiology, which could be the position in that case of Zimmerman's just mentioned.

In 1951, Lighterman had described three (3) cases of the disease in debilitated patients treated with aureomycin. However, it may have been the debility which predisposed to the moniliasis, not the antibiotic.

Woods et al (1951) reported 25 cases of clinical moniliasis following the therapeutic use of penicillin, aureomycin and chloramphenicol. In vitro studies of four (4) strains of Candida, showed that these antibiotics had no stimulating, or even a suppressing, effect on the rate of growth. They concluded that suppression of bacterial flora co-existing with Candida and competing for nutrition in the same substrate, would most likely be the cause for monilial overgrowth and host infection.

However, Reiches, in the same year (1951), pointed out that there had been work done demonstrating that, in vitro, aureomycin hydrochloride does stimulate the growth of C. albicans, in contrast to Woods et al who had found an opposite situation.

Kligman (1952) stated that C. albicans emerges regularly in abundance in the mouths and gastro-intestinal tracts of those receiving wide spectrum antibiotics. He felt, therefore, that a diagnosis of moniliasis should not necessarily be made if this organism is isolated in the presence of some untoward side-reaction to an undiagnosed general condition.

Bartels (1953) described a case of thrush following prolonged

systemic penicillin and terramycin therapy.

The impression that, since widespread antibiotic use, there has been a seeming increase in the number of yeast-like fungi isolated from patients, is supported by data summarised by Carpenter in 1955. She concluded, after examining cultures from 1939 to 1951, a total of over 18,500, that yeast-like fungi increased from almost 0 per cent to 2.5 per cent. These figures seem low, but it must be remembered that she used only children, in whom, as Lilienthal stated, the presence only of C. albicans is enough to produce thrush.

Hurny (1958) stated that in many infectious processes, chemotherapeutic agents inhibit bacterial multiplication and diminish thereby the manifestation of symptoms, without eradication of the infective micro-organisms. This results in the establishment of a masked chronic process which is difficult to diagnose. It is just the means by which superimposition of candidiasis could take place.

As recently as 1964, Lehner stated that antibiotics, mainly broad-spectrum types, favour over-growth of fungi. It does seem to the author, too, that these drugs predispose to moniliasis, in view of the evidence presented.

In 1951, Woods et al found that avitaminosis B complex seemed to have a predisposing effect in the production of moniliasis. Their observations were purely clinical and, therefore, did not permit conclusions regarding the importance of changes in physiopathologic reactions lowering host resistance to monilial invasion.

Lighterman (1951) in a case of moniliasis concerned with a patient on a long course of aureomycin for some systemic disease,

noticed signs of Vitamin B deficiency, and stated that even when Vitamin B was administered with aureomycin, there seemed to be no improvement. However, when the Vitamin B was administered parenterally, the oral lesions improved or resolved. Therefore, he concluded that aureomycin destroys the intestinal bacteria necessary for the synthesis or utilisation of Vitamin B. Monilia albicans is found in many mouths as a normal inhabitant, as has been demonstrated. If aureomycin destroys the organisms which normally inhibit the growth of oral monilia, fungus virulence potential may increase. As the oral tissues are already defective due to avitaminosis B, thrush may result. Therefore correct administration of Vitamin B complex in conjunction with any necessary aureomycin course of therapy, may eliminate side reactions producing moniliasis.

Bily (1959) stressed that the excessive use of antibiotics is contraindicated and that there must be a predisposing factor in the production of moniliasis, such as riboflavin avitaminosis.

Orban and Wentz felt that it is the lack of the riboflavin element of the B complex that favours the disease and Lehner (1964) agreed.

Simpson in 1951, reported two (2) cases where there existed a possible relation between trauma and the onset of the lesions of Candidiasis. In both cases, the trauma was caused by chronic cheek-biting; dentures were worn in each case.

Nyquist (1952) concluded that the main cause of a denture sore mouth, apart from allergy, etc. is traumatic occlusion: Candidiasis may be superimposed over the denture trauma condition which probably

"opens the gate", as it were, for the entry of C. albicans. It is felt that the fungus could possibly harbour in the pores of the denture, as acrylic is a relatively porous material.

Scales et al (1956) confirmed the opinion of Nyquist that traumatic bite causes "denture sore mouth", regardless of the numbers and types of organisms present in a mouth and that Candida albicans growing in such an area would be just opportunists, as they are in perleche. This author agrees.

Weinstein et al (1960) found that C. albicans could be isolated from the saliva of approximately 80 per cent of 36 patients diagnosed as diabetics (diabetes mellitus) while only 50 per cent of 36 patients with no symptoms of diabetes were able to reveal the fungus.

It would be interesting to see a comparison in the <u>numbers</u>, say, of C. albicans per unit volume in the saliva of diabetics, with the <u>numbers</u> in the saliva of non-diabetics; as mere presence does not necessarily produce the disease.

Lehner (1964) has also found that diabetes predisposes to moniliasis.

Lilienthal et al (1956) found by observation and experimental evidence that hormone imbalance alone may stimulate an infection by C. albicans; e.g. treatment with corticotropin and cortisone. They quoted former experiments carried out on mice to demonstrate the enhancement of the pathogenicity of C. albicans by the use of aureomycin, which increased virulence is also increased by cortisone imbalance.

They also felt that hyperkeratinisation may play a part as a predisposing factor in the aetiology of candidiasis, simply by mechanical protection.

Lelkes (1957) stated that there are many factors of a debilitating nature, that bring about the appearance of the disease. Local causes in the oral cavity are disturbances in the micro-biologic metabolism, minute lesions, contaminated dentures, a decrease in the pH, an increase in the oral temperature by about 3^{o}-4^{o}C, and enzymic decomposition and inadequate secretion of saliva.

An interesting finding is that of Kourilsky et al (1960), who discovered that in 750 patients treated at the Medical Hospital in Paris for various allergies, more than 33 per cent showed the characteristic symptoms of moniliasis. The patients were mainly men between 30 and 60 years of age. The symptoms of allergy included allergic rhinitis, oral and facial eczemas, urticaria, dyshidrosis, angioneurotic oedema, gingivitis, stomatitis, headache and a painful burning feeling in the mouth. Kourilsky called this series of symptoms "the allergic syndrome of moniliasis".

Lehner (1964) also found that corticosteroid imbalance, spontaneous or therapeutically induced, promotes candidiasis, confirming the opinion of Lilienthal et al. He also felt the disease is associated with hypoparathyroidism and Addison's disease.

Pregnancy, he felt, disposed to and enhanced the development of thrush, as there was such an increase in the fungus present in the vagina during pregnancy which fact would account for thrush in babies whose mothers had the disease present during a birth. When a mother has vaginal thrush, there is 35 times more chance of her baby being infected, than if she were thrush-free (Wagner, 1959).

Debilitating diseases such as leukaemia, malignant tumours and tuberculosis, as well as alcoholism, have also been implicated as predisposing factors. Poor hygiene, especially in association with bottle-fed babies, is another possible condition of predisposition.

4. Histopathology.

Biopsy specimens of oral moniliasis are not usually necessary. If seen, however, the surface epithelium is usually destroyed and replaced by masses of Candida albicans organisms.

Lehner used P.A.S. stain to demonstrate the fungus, which stain colours it red and the cell membrane deep red, while Grocott's method stained the fungus black: both very useful stains, he stated, for recognising C. albicans. He emphasised that artefacts, e.g. the "stringing" of nuclei, are sometimes confused with Candida, and fibrin, too, is a source of error. The use of phosphotungstic acid - haemotoxylin will, however, stain fibrin blue.

Yeast cells are usually found in company with pseudohyphae and it is exceptional to find one form exclusively. Most commonly, yeast cells are located superficially and pseudohyphae deeply in the keratin layer or in the superficial third of the prickle-cell layer, which is invaded by these pseudohyphae at right angles. Sometimes, intracellular oedema in the prickle cells takes place, which can lead to rupture of the cells and thence to separation of prickle cell layers, which, if invasion of leucocytes takes place, may harbour microabscesses. The healing of acute pseudo-membranous candidiasis is associated with the shedding of the plaque and if, on shedding, prickle cell layers are carried with the plaque, acute atrophic candidiasis results (see later).

The corium can be invaded by the mycelia of C. albicans and by leucocytes (Kovacs, 1956). However, the normal accompanying inflammation is usually only light to moderate with some oedema, lymphocytes and plasma cells (Bhaskar, 1961).

5. Clinical Manifestations. (Leading to Diagnosis.)

The lesions of Moniliasis are soft, white patches like "milk curds" or "curdled cream", with red, swollen bases. The fact that lesions are usually multiple, in Bhaskar's opinion, aids in diagnosis. The lesions may occur on any area of the oral cavity, but most frequently are observed on the tongue, the buccal mucosa, the palate, the gingivae, commissures of the lips and the floor of the mouth. In severe cases, the entire oral cavity may be involved (Shafer et al). If the corners of the mouth are involved, to produce what could be termed "monilial perlèche", it is felt that the typical white lesions must be seen. White patches are fairly adherent, but may be stripped away leaving a raw, painful erythematous surface. From time to time, patches may vary in size and in location.

Conant (1948) stated that oral lesions may last for several years and that Moniliids, which appear on the body as a result of sensitivity to the yeast-like fungi found in lesions elsewhere on the body, occasionally accompany localised infections. These moniliids are quite sterile. Chronic latent oral moniliasis presents an important therapeutic problem, according to Robinson and Tasker (1947). They found reports of the development of "leukoplakia" (hyperkeratosis) and epithelioma in chronic latent oral moniliasis of the adult and stated that these findings would indicate that this disease should be

classified as precancerous.

The author wonders here whether the condition was not hyperkeratosis from the start in these cases. Then again, in long standing lesions, irritation could produce malignant change, perhaps.

Simpson (1951) felt that lesions may be either membranous or of a granulomatous nature, the membranous lesions of acute mycotic stomatitis being called "aphthae" by Kovacs (1956).

Lilienthal et al (1956) said that oral moniliasis presents certain well-defined characteristics, such as tenderness of the area involved and angular cheilosis. In severe cases, the whole of the oral mucosa may be involved. They found, in some cases, lesions of the scalp and nails. The patient's general condition, they felt, was not disturbed, although it is often inconvenient and may even be disfiguring.

Lelkes (1956), investigating the possible sites of candidiasis at the Dental Institute of the University of Budapest, found that moniliasis occurs frequently below dental prostheses, on the tongue and at the corners of the mouth.

Bily (1959) felt that moniliasis of the oral cavity could be divided into three (3) types:- monilial stomatitis (or thrush), monilial glossitis, and perlèche; a "site" classification. The author feels that this is quite a superfluous classification, it being clear to state, say, "general oral moniliasis" or "moniliasis of the buccal mucosa" etc.

Lehner (1964) spoke of the "several forms of candidiasis in the mouth". He found that they responded to different treatment. He outlined them as:

(1) Acute pseudomembranous candidiasis is found in infants and cachectic adults - the white plaque is surrounded by erythema and appears rapidly; it usually can be removed and is asymptomatic. It may clear up spontaneously or with the aid of gentian violet or nystatin. Microscopy demonstrates a superficial scanty invasion of the epithelium with fungal hyphae, with or without a mild inflammation of the corium.

(2) Acute atrophic candidiasis may follow the acute pseudomembranous variety or be present in persons hypersensitive to the fungus. The mucosa is fiery red and pain commonly is present. Nystatin is helpful.

(3) Chronic hyperplastic candidiasis is found mostly in children, skin and nail lesions being possible prominent features. The thick white plaque is firmly adherent and there is no attendant erythema. The disease is resistant to a great variety of drugs (only amphoterin B has been found effective) and it has not uncommonly proved fatal.

(4) Chronic atrophic candidiasis affects solely the denture-bearing area and commonly is known as "denture sore mouth". The persistent erythematosis and atrophic mucosa can be alleviated by a new denture or nystatin treatment.

Chronic moniliasis can be found in a generalised form in a few patients as a complication of a debilitating disorder and eventually may prove fatal (McCarthy and Shklar). The lesions contain less exudate than the acute form.

It can be seen from this section on clinical manifestations and classification that the disease has been divided into several types at the expense of simplicity. The author feels that "candidiasis" is quite sufficient for the primary infection, but that this primary condition must be proven. In "denture sore mouth" the condition is secondary to a traumatic condition of the mucous membrane of the palate. Atrophic candidiasis of the acute type may also be an inflammatory process favouring the proliferation of Candida albicans; not a primary condition. It is felt that the white membrane must be present for a diagnosis of primary candidiasis, and that "acute" or "chronic" moniliasis, plus normal information as to site, etc. is all that is needed in description.

Twenty one (21) out of thirty four (34) patients examined by Lehner (1964 B) had a yeasty odour in their mouths, which was quite characteristic: he termed this "yeast halitosis". Miller (1957) also mentioned a characteristic monilial mouth odour.

Lehner found that thrush often disappeared spontaneously and this can be associated with improvement of a patient's clinical state of general health. When the plaques are thus shed, the denuded erythematous mucosa may give rise to severe pain.

6. Diagnosis.

In discussing the signs and symptoms of Candidiasis, Moore (1957) said that diagnosis is made:

(1) By the appearance of the lesions,

(2) By being able to strip off the white patches,

(3) By straining the material removed with methylene-blue or treating it with 10 per cent K O H (20 per cent is the figure given by Shafer, Hine and Levy) which will show up the monilia forms under the microscope, i.e. the presence of numerous budding cells and filaments in the smear.

Shafer, Hine and Levy adding,

(4) By a positive culture of the material in a medium such as Sabouraud's broth, blood or cornmeal agar.

and McCarthy and Shklar also requiring,

(5) Elimination of other diagnostic possibilities.

Schamuschula (1964) felt that a sensitive technique for the detection and simultaneous identification of the organism would be of service in diagnosis, as well as investigations concerning the development and nature of the lesions. He considered that a technique known as the "fluorescent antibody technique" met the former requirements and he successfully applied it to the detection of C. albicans in oral smears. In this method, Candida albicans is seen as a fluorescent apple-green organism under the microscope, against the light mauve-orange fluorescence of the background material.

Schamuschula felt the early diagnosis of moniliasis was urgent as two (2) cases recently seen at the United Dental Hospital of Sydney had developed malignant change in the affected tissues.

7. <u>Differential Diagnosis</u>.

The majority of plaque-like white lesions of the oral mucosa cannot be stripped away, as can the exudate of thrush. The former

would be the hyperkeratoses, lichen planus and leukoedema. Mucous patches, aspirin burn and any exudation may be confused with thrush, but a positive culture and smear for C. albicans will settle the issue.

Thoma and Goldman (1960) said that thrush in the posterior oral cavity or fauces may resemble diphtheria clinically, except for diphtheria's more extensive distribution, although they admit that thrush can be very extensive. Again, a culture and smear test is indicated.

Experiments were carried out, using mice, by Bichel and Stenderup (1956) to investigate whether infection caused by C. albicans, alone or associated with antibiotic therapy, had an inhibiting effect on lymphopoiesis. The experimental infection produced pronounced lymphopenia in most of the mice. Figures are not given - however, diffuse atrophy of the lymphoid tissue was not observed.

The author feels that nothing obviously valuable was produced from the results - it was felt that it could be employed as another diagnostic test for systemic thrush if any specific result had followed.

8. <u>Therapy.</u>

It is felt that the prime requisite in therapy is the elimination of any predisposing factors in the production of the disease, such as control of diabetes, correction of nutrition, elimination of smoking, alcohol, etc.

In new-born infants with thrush, a thorough swabbing with the mother's saliva to promote the growth of organisms other than C. albicans is good procedure in treatment (Hürny).

In 1948, Conant was recommending a 1 per cent solution of gentian violet in 10-20 per cent alcohol, used up to 3 times per day for four (4) to five (5) days, applied topically, and found it quite effective. However, he stressed the occasional intractibility of moniliasis. McCarthy and Shklar, however, recommended a 0.5 ($\frac{1}{2}$) per cent solution (aqueous), feeling that a 1 per cent solution is likely to produce local reactions.

Reiches (1951) found antihistamine ointment gave "immediate" relief in cases of thrush, so that this ointment could be applied to the mouth, but only in angular cheilosis cases or skin involvement, as it would not adhere to mucous membrane.

In an article "Cases and Comments" of the Journal of the American Dental Association, 1955, treatment advised, of a reported case of moniliasis, was the application of 10 per cent sodium caprylate or 1 per cent gentian violet, three times per day after meals, having first sponged the lesions with a 10 per cent solution of sodium sulphite, in which case the fungus is more readily removed by scraping. Other forms of therapy recommended were roentgen and ultraviolet radiation or a high vitamin diet reinforced with Vitamin A up to 150,000 units daily, massive doses of Calciferol to 100,000 units daily and a saturated solution of Potassium Iodide, up to 2 drops, three times per day (Monilia Infection of the Gums, 1955). The systemic therapy recommended by Orban and Wentz is similar, except that in the case of potassium iodide, the latter recommended a dosage of up to 300 drops per day, watching, of course, that there was no systemic reaction.

However, McCarthy and Shklar (1964) felt that no successful, safe, internal medication is available at the present time. They recommended as suitable local therapy, "Naprylate" and "Chlordantoin".

In 1955, Lilienthal stated that there was no suitable agent available to combat the causal organism of moniliasis, C. albicans. Recommended treatments then were a diet of high calorie and vitamin content, small transfusions of whole blood, local gentian violet or acriviolet, removal of the membrane and treatment of the area with Gram's solution followed by 20 per cent sodium caprylate - also Roentgen ray therapy, but the disease was very refractory to treatment and results were not encouraging. It can be seen, therefore, that in 1955, therapy recommended by clinicians in America was very similar to that being recommended in this country. Lilienthal (1955) showed that C. albicans was completely resistant to all available antibiotics of the time, but that merthiolate one (1) in 1,000 aqueous solution was an adequate inhibitor of growth of this fungus. He felt it could be an aid in root canal therapy when C. albicans is found; in conjunction, of course, with other agents.

Scales, in 1956, said that the mode of treatment was a problem and very few agree as to the best method of therapy. He quoted Cohen and Persky who had shown that thrush in infants had been aggravated when gentian violet was used as a treatment, describing additional glossitis and a glistening pearl-like lesion due to drug irritation.

The author feels that this reaction could be due to the strength of the gentian violet and also to the vehicle, as has been advised earlier in this section by McCarthy and Shklar.

Scales again quoted Cohen and Persky who stated that good results are obtained using Sodium Caprylate, in a study of infants aged from 3 days to 12 months of age. Bily (1959) used 10 per cent Sodium Caprylate solution applied four (4) times per day and claimed that C. albicans was eliminated within one week. This latter result was the best reported, as can be seen from previous information on the use of Sodium Caprylate.

Cohen and Persky also demonstrated that fatty acids, in general, are good fungicides. Scales (1956) as a final statement vowed that "there is no known cure for lesions due to C. albicans".

In 1956 a possible method of treatment of candidiasis was explored by Kovacs, who, in the Dental School of the University of Budapest, carried out an experiment in which 716 implantations of animal placenta tissue were used on the tissues of 179 affected patients. Only 68 patients were re-called, among whom 16 showed no improvement, 25 slight improvement and 27 were "cured". Most arthralgias or cephalalgias decreased or disappeared during or after histotherapy.

Stenderup et al (1957) discussed Wolff's previous successful treatment of two patients for oesophageal moniliasis with a diamidine (Hydroxystilbamidine). Knowing that Stilbamidine and Pentamidine had been shown to inhibit growth of C. albicans, Stenderup found a similar good result using Pentamidine, but stated that Hydroxystilbamidine, as used by Wolff earlier, seemed more effective. Wagner and Kessel (1959), following the above successes with Hydroxystilbamidine, stated that additional and supportive therapy should be used, varying in type

according to the complication, if any, present. Difficulties of feeding are obvious in instances of thrush, as is the need for oxygen in lung involvement. In severe instances, oral feeding must be stopped and intravenous therapy used until lipiodal swallow examinations show that the patient is able to swallow properly.

Nystatin, which has antibiotic effects in vitro against certain pathogenic fungi, was used by Wright et al (1957) in the treatment of 42 patients with oral, 17 with vaginal and 63 with cutaneous forms of moniliasis. The results were considered excellent in 53 of the 122 patients, good in 64 and fair in 5. There were no instances of irritation or sensitisation. In 52 of the patients, the fungus remained demonstrable after healing, yet relapses were infrequent. The patients, in whom results were only fair, had severe systemic illnesses or were under prolonged antibiotic therapy.

Nystatin was applied topically to the skin in ointment form. An aqueous two (2) per cent procaine hydrochloride and 0.25 per cent Polysorbate 80 solution, containing 100,000 units of nystatin, was found very good, but if 2.5 mg. of Hydrocortisone per cc. were added, faster healing took place.

Thrush lesions usually were healed within 2 or 3 days, although, at times, 2 or 3 weeks were required for a cure, clinical effectiveness being influenced by the type of vehicle which was used for the nystatin. When used in ointment form to treat intertriginous areas, the results were poor and yet when in solution, these same lesions rapidly cleared. Apparently, intimate contact between drug and tissue was essential.

Nystatin (or Mycostatin) was discussed by Moore (1957) in an article on treatment of Moniliasis. The drug is derived from cultures of Streptomyces noursei, as is also the anti-fungal drug, Actidione.

Nystatin inhibits or kills all species of fungi and yeasts tested, except actinomycetes, but is inactive against bacteria. It is poorly absorbed from the intestine and is more effective against growing fungi than the spores. It works best by direct contact. The usual dose is about 500,000 units, 3 times per day; the dose can be doubled without side effects and is most stable in powder form.

In very young infants, Mycostatin can be administered in powder form, using honey, which helps to overcome the bad taste and also to make it stick to the tissues, - the honey also holds the Mycostatin powder together. Moore recommended the administration of Vitamin B to overcome any predisposing cause. However, Lehner (1964B) gave Vitamin B complex to nine (9) patients by intramuscular injections without apparent result. Indeed, episodes of thrush actually set in during Vitamin B therapy.

Graham (1960) treated 55 infants under one (1) year of age for Thrush: of these, 26 were treated with gentian violet 1% and 29 with Nystatin, topically applied, four (4) times per day after feeding. Of the 26 infants given gentian violet treatment, eight (8) were free from infection within a week, eight (8) more within two (2) weeks, four (4) did not respond, three (3) had a recurrence after treatment and three (3) defaulted. Of the 29 treated with Nystatin, twenty two (22) were free from infection within a week and six (6) more within two weeks. The mothers reported that the white patches disappeared

dramatically, often within two (2) days and sometimes after two (2) applications only. Relapse occurred in one child, but none failed to respond and there were no defaulters. Most of the infants were less than one (1) month old and most occurrences were in the colder months of the year. In only two mothers and one (1) infant was there a history of recent antibiotic therapy.

Nystatin proved to be non-irritant, non-staining, non-toxic and non-allergic. It was easy to use, whereas the gentian violet had obviously difficult problems, especially in such young children.

The treatment by Nystatin was in oral doses of 500,000 units three (3) times per day. The excellent results here confirmed those of Wright and Moore obtained in 1957, as reported earlier in this section.

Lehner (1964B) obtained similarly good results using Nystatin and the best method of administration was found to be four (4) times per day, using tablets each of 100,000 units, retained in the mouth until disappearance. Lesions mostly disappeared clinically within three (3) days. But this method could not be used for the very young.

Kutscher et al (1959) and again in 1960, discussed the properties of a new adhesive-vehicle preparation designed especially for the application of drugs to the oral mucous membranes, and this vehicle adhered to the desired site for a period varying between one-quarter to two hours. Since all materials placed in the mouth are generally swallowed, any systemic activity which a vehicle may possess, must be considered. Gelatin, Pectin and Carboxymethyl Cellulose in a mineral

oil-polyethylene base, the constituents of this vehicle, have all been found relatively free of deleterious properties in every way. However, the use of this vehicle, known as "Orabase", without any "medication" resulted in a local protectant action by the vehicle itself.

Amphotericin B was tested by Campbell et al (1960) in its effect against 93 strains of Candida. It was active in some measure against all strains, some in a very marked way, others to a less extent. At present, there is an urgent need for basic comparative studies of Amphotericin B and Mycostatin (Nystatin) under controlled conditions. Nystatin has an offensive taste and therefore Amphotericin B is the drug of choice in topical oral application. Each may possess its own particular potential for countering certain strains of organisms.

It is well here to describe, very briefly, the source and properties of Amphotericin B. It is produced by a hitherto unidentified species of streptomyces; the chemical structure is unknown. The pure antibiotic is highly stable. No strains of C. albicans have, as yet, been found which are resistant to it. It is very "safe" since it is non-absorbable from the gastro-intestinal tract and is safe in dosages greatly in excess of the minimal amount utilised in topical oral therapy.

Roland et al (1958) had already used Amphotericin B in "Orabase" in the treatment of a case of denture sore mouth and angular cheilosis with moniliasis, identification of the fungus being obtained by swab cultures. The Amphotericin B, in "Orabase" was applied to the mucous membranes four (4) times per day, in this case conveniently under

dentures. It was applied as a 2 per cent ointment, in "plastibase", to the corners of the mouth. The Orabase, helped by the dentures, increased the potential effectiveness:

1. by maintaining a higher concentration of the drug at the required site;

also it would,

2. decrease the total drug amount needed;
3. increase the duration over which the material will remain in situ;
4. decrease the amount of material which, following displacement from the area, would be swallowed and would thereby be available for systemic activity which was not required here.

As an added aid, the dentures were stabilised by the Orabase.

After a week, considerable improvement was noted and the treatment was confirmed. After a further week, more improvement had been made, but the rate of improvement had decreased. An anti-inflammatory agent, 9,21-difluoro-21-desoxy-hydrocortisone, or F.F.F., was therefore decided upon, to reduce any non-specific inflammation.

Pagano-Levin Medium cultures were taken prior to F.F.F. therapy - no growth of Candida was shown, care having been taken that no Amphotericin B had been applied within a period of at least several hours before swabbing. F.F.F. therapy and Amphotericin B were now used alternately and four (4) days later, the angles of the mouth were normal, as was the palate, and this "healed" condition continued while new dentures, to restore a correct bite, were constructed.

Three (3) weeks later the patient presented with severe herpetic lesions of the mouth and nose, but no sign of any thrush. The herpetic condition cleared after treatment, in ten (10) days.

This case has been dealt with by the author rather fully,

1. to give an outline of treatment;

2. to question why the herpetic condition had appeared. Is it possible that this drug in its turn, has upset symbiosis of mouth flora and the herpetic "sores" appeared?

Diagnosis, in this case, should be "denture sore mouth of traumatic origin and perlèche, over which was superimposed moniliasis". It is important, in cases like these, <u>to ensure adequate diet</u>.

Kutscher et al (1964) used Amphotericin B again in the treatment of 33 patients, all of whom either suffered a primary moniliasis or a secondary one as a result of closed bite, hypovitaminosis, local irritation, etc. The drug was found to have been either suppressant or curative in all cases, removal of the initial, basic condition or predisposing condition being essential first, if complete cure is to be obtained.

9. <u>Conclusion</u>.

To illustrate how serious Moniliasis may be, the author would like to draw attention to a case history by Reade (1964).

An aboriginal girl of 12 months of age was presented for treatment of moniliasis, which had been present for at least one (1) month before examination. Her mother was antagonistic to treatment. However, gentian violet, 1% aqueous solution, was used and seemed to be very efficacious, so anti-fungicides were not employed. However, the

condition suddenly deteriorated and penicillin was given to counteract possible secondary infection. The weather was extremely hot (105°F+) and the child continued with a pyrexia and high respiration and pulse rates, with dehydration, for which glucose/NaCl (sodium chloride) solution was administered by mouth and sponging and a cool fan were used, and sedation instituted by the use of one-half grain Phenobarbitone. The poor child became photophobic, cerebral involvement became apparent and death supervened. Lack of co-operation on the mother's part had been a barrier to a successful outcome. No post-mortem was performed, so it is difficult to judge here the cause of death, - it could have been either dehydration, moniliasis involving the lungs or gastro-intestinal tract, or a secondary infection.

It is felt that the use of an antibiotic could be the worst treatment if, by its employment, monilia were allowed to spread overwhelmingly. Certainly a debilitated, undernourished child must be affected by the extremely hot weather. Perhaps the antifungicide would have supplied the means to a cure. It is interesting to note here what Wagner and Kessel (1959) found in relation to generalised moniliasis. They stated that the disease may spread directly to the oesophagus or, by an unco-ordinated swallowing process associated with thrush of the posterior pharynx, inhalation of food particles may take place, leading to a possible broncho-pneumonia. This syndrome is present if an infant with oral thrush shows toxic reactions, becomes dehydrated, has difficulty in swallowing and chokes during eating, developing cyanosis. Within a short time broncho-pneumonia develops and, without active treatment, death may follow. This description, it

is felt, applies to the case described by Reade.

B. GEOTRICHOSIS

Shafer, Hine and Levy have the only reference to this disease seen by the author, despite diligent search.

It is a fungal disease, similar to moniliasis in its clinical features, but caused by organisms of the Geotrichum species.

Differentiation is made only by microscopic examination and/or culture of the organisms, which are small, rectangular-shaped spores, measuring approximately 4 x 8 microns, often with rounded ends.

Treatment: is non-specific and there are insufficient data on the effects, in Geotrichosis, of drugs used in treating Moniliasis.

C. SYPHILIS

1. Introduction.

Few dentists to-day see the protean oral manifestations of Syphilis. Bradlaw (1958) stated that because of improved diagnosis and modern chemotherapy, few young dentists have ever seen Syphilis at all. Without doubt, many early lesions occurring now could therefore go unrecognised, Bradlaw finding that 35 per cent of all chancres of the fingers occur in dentists, who are probably dealing with unsuspected patients. McCarthy and Shklar (1964), however, have seen occasional "flare-ups" of the disease and warn about complacency, as the disease can apparently re-appear spasmodically. They felt that chemotherapy for other ailments, running a course concurrently with Syphilis in the same patient, may mask the symptoms of Syphilis,

without really treating it; so that sufferers may not show early manifestations, but rather show serious tertiary or "late" symptoms.

The disease can produce a greater variety of manifestations on the mucous membrane and skin than any other infection, and may mimic the signs and symptoms of a wide variety of systemic diseases.

Syphilis is included in this review because of the mucosal white lesions which it can produce in the secondary stage. They sometimes appear on the oral mucous membrane and are known as "mucous patches."

The disease is initiated, in the opinion of nearly all writers, following sexual intercourse, in approximately 95 per cent of cases, although it may be innocently acquired by persons, such as dentists, working on infected persons in a contagious stage (Shafer, Hine and Levy).

2. Incidence.

Although the incidence of oral lesions in secondary Syphilis is quite high, many are transitory and may not be noticed. They may occur before, with or after a cutaneous rash and have been reported as presenting eight years after the primary lesion. Both sexes are affected without any predisposition, although acquired syphilis would occur after puberty usually.

Hendershot (1963) reported that during 1961-2, 18,781 cases of infectious syphilis were reported in the one year in the United States of America, which was three times as many as in 1957 and the highest total since 1950. Other figures confirmed that syphilis was increasing till 1962-63, the last census. Furthermore, Hendershot

felt that the figures were gross under-estimations, as it was likely that 50 per cent of the cases treated by physicians were not reported to public health authorities, as well as, in the author's opinion, the number who would not seek treatment for a long time after their first realisation of their condition. Most cases seem to be in the age group below 25 years when first reported.

Hendershot stressed that the dentist should become more suspicious of oral lesions with which he is confronted, Beerman (1957) having stated that the dentist is often the first to note pathology in the mouth as a manifestation of this disease.

3. Classification.

Syphilis may be either "congenital" or acquired. However, it is felt that the term "congenital" alone, is not explicit enough: a truer definition would be "acquired syphilis congenitally", as congenital syphilis is really "acquired", being an infection initiated, in utero, through the blood stream of an infected mother. This initiation takes place not before the 18th week (approx.) of intra-uterine life. "Pre-natal" syphilis seems to the writer to be a better description for "congenital syphilis".

The clinical course of acquired syphilis may be divided into four stages:

1. Primary
2. Secondary
3. Tertiary (or late)
4. Latent.

It is the secondary stage in which white lesions of this disease manifest themselves in the oral cavity.

4. Aetiology

Fritz Shaudinn first identified the organism which to-day is known as Treponema pallidum, an anaerobic spirochete, - the cause of syphilis (McCarthy and Shklar). Treponema pallidum averages 7 μ in length and has six (6) to fourteen (14) windings. Its "movement" is said to be characteristic, being divided into three (3) elements:

1. A motion of translation in the direction of the long axis;
2. A spiral rotation like a corkscrew on its own axis;
3. A side-to-side waving motion.

Repeated attempts to culture the organism have failed.

Muir stated that with very few exceptions, the disease can be successfully transmitted only by scarification of a squamous epithelial surface in experiment, or through direct inoculation of skin or a mucous surface covered by squamous epithelium, through some crack or abrasion in real life. It would appear almost as if some quality within the epithelial cells were necessary for the initial maintenance of the organisms: "subcutaneous inoculation in apes, for example, fails to produce the disease."

5. The Clinical Manifestations of Acquired Syphilis:

It would be as well to mention here briefly the pertinent facts of the primary stage before coming to a discussion of the oral white lesions found in the secondary stage.

Incubation following contact with T. pallidum varies between 12 and 40 days and may be greatly disturbed because of inadequate

chemotherapy at some time during the normal incubation period.

Syphilis may be acquired without showing the primary lesion, but it is more usual to develop a primary, the most frequent oral site for which is on the lips, mostly the upper, the tongue or the tonsillar region. This primary lesion, or chancre, is an ultimate painless ulcer with considerable peripheral induration, and unilateral regional lymphodenopathy of marked proportions is a significant finding. Both chancre and lymph nodes teem with spirochaetes, which should be verified under dark-field examination. Shafer, Hine and Levy stressed the importance here of a dark-field examination of lymph nodes rather than the chancre, as Treponema microdentium and/or T. macrodentium are so often present in the mouth normally and may be confused with T. pallidum. Serologic tests for the disease start to become positive at chancre appearance time and by the third to fourth week are definitely positive.

The Secondary Stage commences at about the 6th to the 8th week after infective exposure. The clinical symptoms commence with an influenza-like syndrome, general eruption on areas of the skin and mucosal surfaces and lymphadenopathy, which phase may last up to a year.

Mead (1940) described the onset as being recognised by slight fever, with a temperature of up to 102° F., restlessness, general malaise, headache, shedding of hair, anaemia, sore throat (because of the mucous patches) and general joint pains. There can also be a gingivitis, iritis and/or otitis media. A syphilitic sore throat is

very common, affecting the nose, pharynx, tonsils and larynx in a diffuse inflammation, in grade from a slight reddening to an extensive diphtheroid involvement with a pseudo-membrane and necrosis with sloughing.

The mucous patch is considered the typical lesion, with usually, concurrent skin macules and/or papules.

Bradlaw stated that a diffuse and transitory erythema is the earliest oral lesion of generalised syphilis and is most often seen on the hard and soft palates, buccal and labial mucosae. The mucous patch follows.

Fiurama et al (1957) felt that mucous patches and lesions of the tongue, tonsils and pharynx are those most to be looked for; apparently they found that these are the usual sites of occurrence. The mucous patch is slightly raised with a smooth central erosion covered with a faintly grey-white delicate membrane, which, when removed, leaves a clean, flat, erythematous base - the lesions are relatively painless and between half (½) and one (1) cm. in diameter. They may occur without any erosion of the surface at all, in which case the palate is the usual site. When occurring at the corners of the mouth, the papules or macules may become fissured because of the stress of opening the mouth. These lesions are referred to as "split papules".. (McCarthy and Shklar).

The author feels this could be an aid in diagnosis.

All oral lesions of secondary syphilis are highly contagious because of the high incidence of T. pallidum therein. If the lesions

are eroded and become confluent, the classical "snail-track" appearance can be produced (Fiurama et al).

Bhaskar (1961) recorded that mucous patches may be the only manifestation of secondary syphilis. He said the most common sites of oral occurrence were the tongue, lips and the tonsils, but they can occur anywhere in the mouth. Rarely, too, wart-like growths, called condylomata, may appear in the mouth and these may manifest as white lesions. They are slightly elevated and the surface is roughened.

Thoma and Goldman stated that the mucous patches are recognised by multiplicity, rapidity of onset and the oval shape with an indefinite are of inflammation round each one. They are not painful, but may become sensitive from irritation. Reactions to Wasserman (complement fixing) test and precipitation tests are positive.

Burket found mucous patches on genital mucosa and oral mucosa, but not on the gingivae. He felt they were the most infectious lesions of acute syphilis and appeared as slightly raised, greyish-white lesions surrounded by an erythematous base. He said they are moderately painful on <u>movable</u> tissue (i.e. tongue or cheek). They are usually associated with dermal lesions, but can be mistaken for healing herpetic or traumatic lesions.

The accompanying dermal rash is described by Mead (1940) as typically slight reddening of the skin (roseola) and the rash gradually develops into small distinct spots, becoming slightly raised, firstly papules, then pustular and finally ulcerative. All may exist together on the face, chest, back and the extremities.

It can be seen, therefore, from the above descriptions, that all writers are in basic agreement in regard to the clinical manifestations of these lesions.

McCarthy and Shklar stated that as this secondary stage disappears, the patient is again symptom free and the positive serologic tests for syphilis are the only demonstrable signs of the disease and this may continue for many years, the blood tests becoming gradually negative. This is the latent stage. However, late or tertiary manifestations may appear at any time following the secondary stage.

Interstitial Glossitis is the most characteristic and important change in oral syphilis, according to McCarthy and Shklar. In this, a bald tongue is produced by atrophy of the papillae, which course occurs by reason of the spirochaetal obliterative endarteritis of the tongue, leading to ischaemia of the papillae and thence to atrophy. A wrinkling of the tongue surface is caused by muscle atrophy. The normal protective surface having disappeared, hyperkeratosis takes place in order to re-establish protection and this condition may lead to malignant change.

It is interesting to note here that, in Wynder's (1957) report on the aetiology of mouth cancer, among a single group of 59 men with multiple primary cancer, one of which sites was the oral cavity, eight (8) had a history of syphilis, cancer occurring on the anterior two-thirds of the tongue or on the lips in most patients.

Fiurama (1957) said that in late syphilis, a multilobulated tongue with atrophy and hyperkeratosis is seen, often associated, at

this stage, with a perforated palate. However, Taylor and Hipple (1961) felt that the oral lesions of tertiary syphilis are generally confined to the palate as gummata and rarely present a diagnostic problem. Oral lesions, they felt, of tertiary syphilis are uncommon.

Mead called the glossitis of syphilis a sclerosing one, which he said may be superficial or deep. In the superficial type, indurations are deep red and occur in various sizes and shapes, tending to breakdown and when healed, leave milk-white patches. Could this be simply the atrophic glossitis with hyperkeratosis previously mentioned?

The disease, when at this very chronic stage, can, according to Burket, produce a tongue movement which is very greatly impaired and the author feels that this would be as a result of the deep sclerosing glossitis mentioned by Mead.

6. Diagnosis.

(a) Histopathology. Although not diagnostic, it may be helpful in differential diagnosis. There is a perivascular infiltrate with lymphocytes and plasma cells. Endothelial oedema of both the superficial and deep blood vessels is apparent (McCarthy and Shklar).

Bhaskar said that condylomata, under the microscope, reveal a dense infiltrate of lymphocytes, plasma cells and macrophages, with a covering of hyperplastic epithelium.

(b) General. As mentioned before, when primary or secondary lesions are present, dark-field examination for T. pallidum is the best diagnostic procedure. Serologic tests are used for corroboration

of a clinical diagnosis of syphilis, but they can remain positive long after active syphilis has disappeared following successful treatment; however, spinal fluid examination, Reiter's protein complement fixation or T. pallidum immobilisation tests will give only true positive reactions, as they are specific for T. pallidum antibodies.

A past history of exposure and infection is important.

7. Differential Diagnosis.

Lichen planus and drug burns and eruptions are likely to present lesions that resemble the mucous patch clinically. The case history, other evidence of rashes on the skin and mucous membranes and serologic tests for syphilis should establish correct diagnosis.

Pronounced tongue atrophy may be also seen with vitamin deficiencies, anaemias, post antibiotic therapy and lichen planus. A careful diagnosis, without haste, should be made. Hyperkeratosis may resemble the mucous patch and, in fact, syphilis is said to predispose to it. However, serology should decide.

8. Therapy.

McCarthy and Shklar have pointed out that T. pallidum has not yet developed a resistance to penicillin, which is their therapeutic drug of choice, usually administered in doses of up to 600000 units daily for ten (10) days. Patients should be followed up for years after being treated, to keep a check in case of further outbreak. Sometimes, a patient will develop sensitivity to penicillin, in which case broad spectrum antibiotics are usually substituted.

Orban and Wentz (1960) recommended intravenous penicillin injections in massive doses (10 million units) over a five day period. However, if the antibiotic is used alone, relapses may occur. Neoarsphenamine, intravenously, and Bismuth, intramuscularly, may be used as supportive treatment. They stressed, also, that continued blood-tests be made to check for negative results.

However, McCarthy and Shklar stated that the serologic tests may remain positive throughout life, despite successful treatment, so a complete history of their particular case should be given to each patient to avoid unnecessary concern if examined later for other disorders. A cure should be judged, if positive serologic tests are continually being obtained, on titer and on clinical grounds.

Taylor and Hipple (1961) felt that many cases of syphilis are given inadequate doses of penicillin in the primary stage. When this does occur, it seems likely that the inadequate treatment may mask the infection, which produces no secondary symptoms, but does not prevent the development of gummata.

It seems that in cases where serologic examination continues to be positive, despite massive doses of penicillin originally, apart from negative clinical symptoms and possibly titer, there is no absolute proof that the infection is cured. For in many cases of latent syphilis, no clinical symptoms manifest over long periods, until the tertiary stage gummata manifest themselves. The author feels that constant and continued patient surveillance would be essential.

9. Congenital Syphilis.

There is little mention in any of the articles reviewed in

journals or in text books that congenital syphilis produces white lesions, - but they can occur. A point of interest, however, is made by Swallow (1962) who, mentioning the usual triad of Hutchinson's teeth, interstitial keratoses and eighth nerve deafness, states that the incisal notch in some cases of Hutchinson's teeth is not present, although a semilunar defect may be seen instead. He felt a notch could appear later, but that the wedge or "screwdriver" shape of the incisors, not the notch, is the chief characteristic.

Cohen (1954) felt that reliance on a single negative serologic test during pregnancy and/or inadequate therapy could be responsible for the continued occurrence of congenital syphilis.

D. FORDYCE'S DISEASE

Syn. (Fordyce Spots. Pseudocolloid of the Lips. Fordyce's Granules)

This condition, which is not a disease, is one which manifests yellowish, small macular areas in the mouth mucosa, usually in the buccal area, the retro-molar area and the lips, but sometimes also in the gingivae and palate. Moskow and Baden (1964) reported the finding of Fordyce Spots in the gingivae. Close inspection of the involved areas will occasionally reveal duct openings from which a greasy substance, sebum, may exude. They are ducts of ectopic sebaceous glands that are in close relation to the covering epithelium and can be found in about 80 per cent of the population. It has been stated that the disease was first described by Fordyce in 1896 (Burket,1961). However, Moskow and Baden, after a review of the literature, credited

the first description to Kolliker, 45 years earlier than Fordyce. The spots are without clinical significance. Burket (1961) said the glands are hypertrophic, probably the result of the trauma of chewing, irritation from smoking, bacteria or a combination of these factors and added that the lip lesions are often very marked in tobacco smokers. The individual lesions are usually discrete and not great in number, but when high in number and close together, may form quite large, irregular yellowish plaques, which are said to look like chamois skin. In an exhaustive study, Miles (1958) found symmetry in distribution, size and numbers of the glands, with little correlation between the prevalence of glands on the lips and on the cheeks. On the cheeks, the glands are most commonly found in small clusters in the region of the opening of the parotid duct and immediately lateral to the angle of the mouth. The majority of authors called the gland structure normal, not hypertrophic as had Burket. The condition is a choristoma, formed when the developing cheeks are fusing from embryonal processes, the glands developing as a result of misplaced anlage. "Dermaplakia" (Sicher) was suggested as the name for the occurrence of sebaceous and sweat glands, as well as hair follicles, in the oral mucosa.

Fewer children than adults exhibit Fordyce's granules, as the sebaceous glands do not reach full development until puberty. It has been claimed that the duct openings are keratin plugged, but this was not proven and it is quite possible that under the influence of the secretion from these glands, they could play a definite part in influencing the oral environment (Chauncey et al, 1959).

The author feels that Fordyce Spots should not strictly be

included in white lesions of the oral cavity, although he has seen the condition included among white lesions in one or two references. The percentage normal occurrence seems so high, could the absence of these glands be abnormal?

Witkop et al (1960) also stated that some cases of Hereditary Benign Intra-epithelial Dyskeratosis presented cream-coloured intra-epithelial plaques of thickened mucosa, "more superficial than the sub-epithelial plaques formed by the coalescence of Fordyce Spots": there does, therefore, seem to be some argument for the inclusion of the condition in this survey.

References: Orban and Wentz (1960): McCarthy and Shklar (1964): Shafer et al (1963): Thoma and Goldman (1960): Bhaskar (1961): Burket (1961): Colby et al (1961): Stones (1962): Chauncey et al (1959): Miles (1958): Haring and Lewis (1961): Halperin et al (1953): Witkop et al (1960).

E. BOHN'S NODULES

Syn. - Epstein's Pearls:

Introduction: Monteleone and McLellan (1964) stated that, "Examination of the oral cavity of new-born infants often reveals the presence of white to yellowish-white nodules of pin-head size located in the region of the junction of the hard and soft palates, immediately to either side of the median palatine raphe. In this location, these nodules are known as "Epstein's Pearls" or "Bohn's Nodules". Despite the last statement, however, they do mention the occurrence of the

nodules on the gingiva, where they are also described under the same names. Bhaskar (1961) also described the lesions as small firm, white nodules occurring on the palate or alveolar mucosa of new-born infants. Shafer et al (1963) referred to them as clinically obvious, small, discrete swellings of the alveolar ridge, sometimes appearing blanched as though from internal pressure, and found in infants.

Jacobs (1956) stated that some infants may present tiny whitish-yellow nodules within, and on each side of, the median raphe of the hard palate. Sometimes they are found on the gingivae. Investigators are of the opinion that these are tiny retention cysts, disappearing about two months after birth. The author stresses that these nodules may not always be clinically obvious.

Nichamin and Kaufman (1963) described a congenital developmental abnormality of the gingiva in the form of clinically visible, multiple microcysts appearing in an infant at three (3) months of age. They remained for twelve (12) months and disappeared without treatment.

The author feels that this little known condition should be further reported so as to bring it before the medical and dental professions; parents may mistake the "pearls" for erupting teeth.

<u>Aetiology:</u> Monteleone and McLellan listed possible sources of origin thus:-

1. Abortive enamel organs
2. Gingival glands of Serres
3. Epithelial debris of the tooth follicle
4. Mucous gland cysts
5. Epithelial buds of the enamel organ.

They felt that the formations are "epithelial inclusion cysts which were incorporated in the embryonic oral cavity and its associated structures during development."

Shafer et al referred to them when they occur on the alveolar ridges as benign gingival cysts, which have become sufficiently large to be seen clinically.

The aetiology of gingival cysts in general, has been variously described as coming from:-

1. Traumatic implantation of epithelium - (Bhaskar and Laskin, 1955; Ritchey and Orban, 1953).

2. Heterotopic glandular tissue (Traeger, 1961).

3. Remnants of the dental lamina, enamel organ or epithelial islands of the periodontal membrane.

4. Degenerative changes in a proliferation from an epithelial peg.
(Ritchey and Orban, 1953).

Shafer et al (1963) believed that the cysts arise from either

(a) cystic degeneration of dental lamina,

or (b) traumatic implantation of surface epithelium.

On this basis, the writer feels that it is most likely that Epstein's pearls originate from cystic degeneration of the dental lamina, as Kreshover, quoted by Shafer et al, stated that all instances of gingival cystic lesions found in the jaws of 65 infants arose from cells of the dental lamina.

Nichamin and Kaufman (1963) quoted D.A. Kerr as saying that gingival microcysts can be seen in the gingival tissues of adults if several gingival sections are examined, apparently remaining quiescent but explaining the appearance of occasionally clinically evident cysts.

Embryology: Monteleone and McLellan wrote thus:-

"Toward the end of the second month in utero, the palate has started its development. Each maxillary process produces a lateral palatine process inside the mouth. These processes are horizontal and shelf-like, growing from the sides of the mouth toward the mid-line and downwards. Between ten (10) and eleven (11) weeks in utero, the lateral palatine processes meet and fuse with each other and with the much smaller premaxillary process and the nasal septum; palatal fusions normally are completed by the end of the fourth month. It is at this stage that epithelium may become trapped between lines of fusion producing these inclusions. After birth, the epithelial strands usually atrophy and become resorbed.

The explanation for Epstein's pearls on or near the surfaces of the gingiva essentially is similar to that of their formation on the palate. During the sixth week of embryonic life, an epithelial thickening arises near the free margin of the jaws; this thickening is continuous and runs along the entire length of the ridge. It is referred to as the dental lamina and is the anlage of the ectodermal portion of the tooth. After it has completed its function (formation of the enamel organ of the deciduous as well as permanent teeth) the dental lamina becomes fenestrated and is resorbed. Remnants of the lamina sometimes persist as epithelial isles which are isolated by rapid proliferation of adjacent connective tissue. The clinical significance of such 'trapped' odontogenic epithelium lies in the possibility that persistent isles may differentiate into cysts, enamel masses, or even supernumerary teeth."

Occurrence and Incidence: Bhaskar (1961) said that Epstein's Pearls occur but rarely, when they are usually multiple and do not increase in size.

Kreshover found in the maxillae and mandibles of seventeen (17) infants, sixty-five (65) examples of gingival cysts, thirty eight (38) multiple and twenty seven (27) single and they were localised in the corium below the surface epithelium. Those in the anterior portion of the jaws were usually displaced lingually with respect to the deciduous incisors and cuspids, while those in the posterior portion of the jaw were found occlusal to the crown of the molars. However, all these cysts were not clinically observable as Bohn's nodules (Shafer et al).

Monteleone and McLellan (1964) inspected the palate in 293 consecutive, healthy term Negro babies, within a day of birth in each case, and found Bohn's nodules on or near the median raphe in 79 per cent of the infants, while in 100 Caucasian infants they found an occurrence of 85 per cent, equally divided between male and female. The usual number of nodules was one, two or three, but occasionally six or seven were counted. Multiple arrangements were rarely the same from mouth to mouth, even in twins. They felt the occurrence is so frequent as to call their presence a normal state, and said that many pearls would be invisible because of their deeper situation.

Histopathology: Shafer et al stated that the "Pearls" are true cysts, since the cavity is lined by stratified squamous epithelium. The gingival cyst is usually filled with fluid, but these Epstein's

Pearls contain keratin (Bhaskar).

Therapy: Because of their superficial location, they are often "shed" spontaneously within a few weeks of birth, but, if absolutely necessary, they could be surgically excised (Bhaskar, 1961).

Kreshover feels that they ultimately disappear.

F. (WHITE) HAIRY TONGUE

Syn. Lingua Alba, Lingua Villosa Alba, Hyperkeratosis of the Tongue.

1. History.

It was in 1835, that Rayer, according to Pincus and Boyd-Cooper (1938), first described the condition, black hairy tongue, Raynaud, in 1869, first suggesting an aetiology of a specific organism. However, Pincus and Boyd-Cooper pointed out at the time that the appearance of this "hair" on the tongue and a black discolouration are not necessarily always associated, and that other colours have been described by Lebar, in 1916, ranging from yellowish to black.

Miller et al (1938) recommended the use of the term "lingua filaceosa chromatica" (coloured filamentous tongue) to replace "hairy tongue", and with this the author agrees, realising that this suggested name is very cumbersome, but agreeing with it if only to change the descriptive "hairy", which has become permanently, it seems, tied to "black". "Furred" or "furry" seems a good adjective, but this is synonomous with "coated" which, in the opinion of the author, is not the same condition as "hairy" (tongue).

2. Clinical

Thoma and Goldman (1960) stated that the condition is easily recognised and is harmless, occurring only on that part of the tongue anterior to the circumvallate papillae, but always on the dorsum. The "hairs", or filaments, may be long and coarse or short and fine, the colour not often being white or yellowish; rather is it more often brown to black. It appears like matted fur or felt, Shafer et al (1963) stating that the papillae may even be so long as to stimulate gagging by touching the soft palate. Generally, there are no subjective symptoms.

Cheraskin and Langley (1956) describing (black) hairy tongue, stated that it is a condition of hyperkeratinisation and hyperplasia of the filiform papillae and that distinction must be made between it and "pseudo-black tongue" which is a simple discolourisation of the tongue due to pigmentation by foods or drugs. In this, McCarthy and Shklar agreed (1964). The writer feels that the "black" appearance is very likely the black discolouration of "pseudo-black tongue", superimposed over the "hairy" formation. In other words "white" hairy tongue is the "basic", shall we say, condition from which the black state, or any other colour state, occurs. One might say that "pseudo-black tongue" is analagous to "coated" tongue (which is usually a creamy-brown), the difference between them being only one of colour.

Mead (1940) said that the whole tongue, or only a portion of it, may be involved in "hairy tongue", that the papillae and epithelium

become a dull white, but that there is no actual fur formation as in black hairy tongue. This suggests to this reviewer that Mead was dealing with a "coated" tongue and not a "hairy" tongue at all. This also applies to Loudon (1956), who referred to "furry" tongues, which adjective could be interpreted as "hairy" and it is felt that this was not implied at all, "coated" tongue being the implication.

Cheraskin and Langley (1956) described hairy tongue as occurring only on the dorsum and always anterior to the circumvallate papillae, as had Thoma and Goldman; Cahn (1941), in agreement with this statement of site, had added that the patch is in the midline: it may be small or elliptical or quite diffuse and the condition rare. Cahn also had stipulated that true hairy tongue resulted from hyperkeratinisation of the filiform papillae, bringing about hair-like elongations. Any darkening, he said, is due to chromogenic fungi.

Shira (1957) stated that the papillae are so numerous in the condition that a lesion resembling fur or felt is produced, the papillae varying in length, being often parted. The papillae have been reported as long as three-quarters (¾) of an inch.

Burket (1961) stressed the harmlessness of the condition, which can disappear spontaneously, but the author feels that, whereas the condition may be harmless, it could be almost unbearable in a sensitive mouth if the papillae were, say, half (½) an inch in length.

3. Occurrence and Incidence.

McCarthy and Shklar (1964) stated that true cases of hairy tongue are rare. Until recently, the majority of their patients were elderly males who smoked and had poor oral hygiene, but recently they

have seen the condition in young females with clean mouths, who were non-smokers and not taking any medications.

In 1939, Prinz and Greenbaum found the condition usually in males, at any age, but mostly in the age group 20-25 years.

Stones (1962) examined patients of all ages with hairy tongue; Bhaskar (1961), however, placed the disease in the adult category and stated that it had a predilection for males. Cheraskin and Langley (1956) and Burket (1961) also found this preference for males, but in the young adult age group, as had Prinz and Greenbaum many years before. Burket said it occurred sometimes in cases of Darier's disease (true).

4. Histopathology

All writers agree that the condition shows hyperplasia of the filiform papillae, with extensive elongation and with masses of bacterial and mycotic micro-organisms between the "hair-like" papillae. Connective tissue inflammation of a chronic nature is present, with lymphocytes and plasma cells invading.

5. Aetiology

Stones (1962) stated that "hairy tongue is due to overgrowth of the filiform papillae which elongate in an area of the dorsum. The cause is not elucidated;" and this sums up the position at the present time, in this writer's opinion.

In 1938, Pincus and Boyd-Cooper said that it is open to question whether heavy smoking, chronic oral sepsis, exposure to X-rays, the presence of malignant growth, nutritional deficiencies or syphilis are concomitants, which was endorsed by Bartels and Millard (1955),

but who found that the elimination of a systemic disease caused an apparent cure, and endorsed also by Shafer et al (1963), who noticed the frequency of hairy tongue in patients who had had extensive X-ray radiation about the head and neck for the treatment of a tumour. The sometimes ensuing hairy tongue, they felt, is due to some change in the local oral environment.

Stones (1962) quoted Oppenheim, who, in 1917, had experimentally produced, as had others, hypertrophy and hyperkeratosis of the filiform papillae by the application of vegetable tinctures and antiseptics. Hirschfeld (1934) stated that most cases coming to his attention were caused by sodium perborate used in the treatment of Vincent's infection, and Miller et al (1938) declared that sodium perborate and hydrogen peroxide, too, were possible causes of oral pathosis (not only conditions of the tongue) and that their use should be followed by rinsing the mouth with water. They felt that systemic effects can result following excessive use of the perborate. Glickman and Bibby (1944) also verified the irritant action of sodium perborate in aetiology of the condition and Bartels and Millard (1955) stated that oxygenating drugs have been shown to cause hairy tongue by local stimulation and again, in 1956, Hine also agreed with this statement.

Michanowicz and Michanowicz (1964) reported a case seemingly specifically due to the use of "Gly-oxide". The condition resolved when the drug was discontinued.

Prinz and Greenbaum (1939) felt the cause is a tropho-neurotic disturbance which electively predisposes the surface of the tongue to irritation, and secondary deposits of pigment then may take place.

Cheraskin and Langley (1958) mentioned a possible congenital predisposition, aggravated by local irritants, Cahn having stated in 1941 that the condition seemed congenital in origin, as he had reported two (2) occurrences in children of 15 months and 4 years of age. Schaffer (1951) also was in favour of a possible congenital cause. If a congenital predisposition exists, it seems logical to the writer that the statements of both Bernier (1959) and Shira (1957) would be reasonable, namely, that food impaction in the irregularities of the tongue surface could cause inflammation and, with the above congenital predisposition, hypertrophy of the papillae may ensue. Shira applied this theory of aetiology, though, more to the "fissured" or grooved tongue, but the writer feels that it could occur in highly susceptible, but normally surfaced, tongues. Once initiated, the condition could be difficult to bring back to normal. Anderson (1957) said the "hairs" are the result of chronic irritation, and that pigment producing micro-organisms on the surface of the tongue cause discolouration. This is confirmed by Cecil and Loeb (1959). Pincus and Boyd-Cooper, however, had stated that there was no proof that the (dis)colouration of the tongue was a result of fungus infection of the hypertrophied papillae.

Stones (1962) said that the affected area can be discoloured due to either chromogenic bacteria or food, tobacco smoking and medicaments. Pincus and Boyd-Cooper (1938) cultured an organism, the colonies of which were black and the pigment of which resembled melanin.

Cheraskin and Langley (1956) presented, as a possible cause of

staining of the "hairs", the iron contained in the blood from gingival inflammatory conditions. It seems to the writer that this would be due to the formation of an iron sulphide: indeed foods containing iron could also be a cause of the stain.

Cross (1949) and Wolfson (1949) both reported that the local or topical use of penicillin produced black hairy tongue. Cheraskin and Langley (1956) also found that locally applied antibiotics had greatly influenced the frequency of hairy tongue by upsetting oral bacterial symbiosis and permitting various fungi to flourish. Thoma and Goldman (1960) stated that the prolonged use of penicillin and aureomycin, whether in lozenge form or not, has been shown to cause black hairy tongue and is probably the most prevalent cause of the condition seen to-day. This is also endorsed by Colby et al (1961) and they added that the antibiotic must be used for a week, at least, before the hairy tongue will appear. However, the condition has been produced much sooner, - in fact in 48 hours, by Wolfson (1949).

McCarthy and Shklar (1964) are of the opinion that antibiotics produce only the discolouration <u>without significant changes in the length of the filiform papillae.</u> They felt that the hyperpigmentation is due to an overgrowth of pigment producing cocci, due to the antibiotic therapy upsetting symbiosis, and when the therapy is discontinued, the condition is allowed to clear: in other words, antibiotics can produce a black tongue, but without "hairs". Shira (1957), however, felt that antibiotic therapy caused a "hairy" condition similar to the idiopathic type of lesion and this is certainly confirmed

in several case histories of Wolfson. McCarthy and Shklar said that the mechanism for the papillary change is unknown, but that it could be logically explained as a result of chronic irritation. They agree with Bartels and Millard (1955) who seem to have proved that the cause of the "hairy" condition is not bacterial, as no pathogenic organism has yet been isolated.

Shafer et al (1963), while granting that the cause is unknown, are of the opinion that micro-organisms, particularly fungi, might be the exciting factor in producing the overgrowth of the papillae. They admitted, however, that it is a fact that many different types of organisms, including Candida albicans, can be cultured from scrapings of the papillae, but there is no proof of a cause and effect relationship, some saying the organisms are simply saprophytes and that their eradication does not necessarily result in a return of the tongue to normal. Fungus aetiology has been suggested as a possible cause of (white) hairy tongue by Bhaskar (1961), but he, too, said the cause is unknown. He mentioned the possibility of an allergy in aetiology.

Tomaszewski (1953) too, felt that idiopathic black hairy tongue differed from that produced by antibiotics, by the appearance or presence of a comparatively rich bacterial flora and by the hypertrophic condition of the filiform papillae, which latter condition helps the proliferation of the bacteria. In fact, Tomaszewski found that locally applied antibiotics could be used to <u>treat</u> idiopathic black hairy tongue with good results. Antibiotics, therefore, do not seem, to some writers, to produce a true black hairy tongue, but a pseudo-black tongue (as

spoken of by Burket), and Hine (1956) stated that this discolouration could be prevented or minimised by concurrent administration of Vitamin B. Colby et al (1961) said that during antibiotic therapy the excessive tongue "coating" is not caused by hypersensitivity, but is related to the predominance of fungi in the oral flora and that when the flora again become balanced, the tongue returns to normal. They then stated that black hairy tongue may develop following the use of various chemotherapeutic agents but that it may also occur without apparent cause, and in these latter cases, tends to be persistent.

Mead (1940) linked a chronic intestinal dyspeptic condition with hairy tongue, associated with a bad taste before the attack. As pointed out, though, in the chapter on "Clinical Manifestations", Mead did not associate white hairy tongue with overgrowth of the filiform papillae, so that this "dyspeptic" cause would be aetiologic only in-so-far as "coating" or colour is concerned. Schaffer (1951) had said that the tongue coating in gastro-intestinal upsets and protracted febrile diseases, can be logically explained on the basis of a decrease in salivary flow and inadequate removal of the continually forming coat, due to abnormal diet and poor oral hygiene. But Schaffer did not confuse a "coated" tongue with a "hairy" tongue.

Stones (1962) and Thoma and Goldman (1960) also mentioned the possibility of gastric hyperacidity as a cause; - but they were referring to the aetiology of actual "hairs" themselves, feeling that the gastric condition in some way caused an irritation to the filiform papillae, resulting in hyperplasia and hyperkeratinisation.

6. Differential Diagnosis.

Prinz and Greenbaum (1939) were concerned that this hairy tongue could possibly be confused with the hyperkeratoses - however, the peculiar milk-white colour and total absence of hypertrophied papillae of hyperkeratosis would almost eliminate it, as well as its rarity in the position where hairy tongue is found. They felt also that the intense chronicity of hyperkeratosis would also be an aid in differentiation, but the writer would not rely on this factor; - both conditions can be chronic.

7. Therapy

Prinz and Greenbaum (1939) recommended the use of 3 per cent hydrogen peroxide applied locally in cases of hairy tongue, but used 10-15 per cent salicylic acid in severe cases, followed by hydrogen peroxide and normal saline. They advised the avoidance of tobacco and oxidising mouth-washes and also those containing tannic acid. Why hydrogen peroxide, an oxidising agent, was exempt from the general oxidising mouth-washes, is not clear. They felt that the scraping of the tongue with a wooden blade to remove debris, and perhaps keratin, was very useful, but it must be followed by a 50 per cent solution of trichloracetic acid upon a dried tongue t.i.d., and any systemic disease must be treated.

Shira (1957) recommended 10 per cent salicylic acid as a mouth-wash followed by vigorous rubbing with 3 per cent hydrogen peroxide.

Stones (1962) recommended cleansing of the tongue twice per day with a mild antiseptic and a tooth brush, then attempting to eradicate

the hairs by scraping, failing which a brief and careful daily application of 50 per cent trichloracetic acid for several days, is of value.

Thoma and Goldman (1960) preferred the use of gentian violet topically and the avoidance of tobacco and irritating drugs. Escharotics, they felt, could be used to cause desquamation, thymol (1:1000) being recommended to control mould growth.

Cheraskin and Langley (1956) felt that good oral hygiene is the only necessary requirement and that if the hairy condition is due to drugs, the discontinuance of those drugs would constitute the best therapy. Both Bhaskar (1961) and Cheraskin and Langley (1956) stated that individuals with hyperplastic filiform papillae would find it necessary to brush the tongue just as one normally brushes the teeth.

Cheraskin and Langley favoured 10-15 per cent salicylic acid as a swabbing agent to remove the "hairs", McCarthy and Shklar using the same agent but in less concentrated form, a 5-10 per cent alcohol solution, which they carefully washed away afterwards. The former workers employed a 20 per cent aqueous solution of sodium caprylate as a fungicide and this, together with nystatin, is also recommended by Burket (1961).

It is interesting to note that Standish and Moorman used podophyllin resin with good results, as reported by Shafer et al (1963).

In 1962, Weinstein and Rosencrans reported the treatment of a 61 years old man with triamcinolone acetonide, after all other treatment

had failed. After four (4) days, the tongue was almost clear, the patient reporting that, after two (2) days, improvement had already been noted by him. After six (6) days from commencement of therapy, the tongue was normal, and taste, which had been affected before therapy with this drug, was normal again. They recommended further trial of the drug. However, triamcinolone therapy, in common with other corticosteroids, should be administered only with the full realization that its action is generally one of suppression rather than cure. It should also be emphasised that triamcinolone acetonide is a fully active (systemically) corticosteroid and that the medicament, when swallowed, is made available for systemic action - a matter of advantage or disadvantage, as the case may be. Therapy must be accompanied by careful observation. The drug is administered orally in orabase (Kutscher et al, 1959), so that it is important to apply it at night when the vehicle will serve its most useful purpose, (Zegarelli et al, 1960). The effect of the drug is either:

1. Suppressant
2. Ameliorative

or 3. Curative (acute conditions.)

(In 1964, Smith treated three (3) cases of papillary hyperplasia with orabase containing no triamcinolone acetonide and these lesions did not show as good a regression of the hyperplasia or of any associated inflammatory process as some which had been treated with orabase containing triamcinolone acetonide.)

8. <u>Conclusion.</u>

The author feels that there are possibly two types of so-called

"hairy tongue":

1. A tongue with long filamentous papillae resembling hairs, the keratin of which would initially present a whitish appearance, but which would stain either slowly or rapidly depending on conditions, the colour also varying according to different local and systemic factors.

2. A tongue without these elongated papillae, yet with staining due to various possible causes already outlined in the preceding descriptions, or with staining due to causes which do not come within the scope of this paper. This "type" then, is not a hairy tongue at all. It could be called "black" - (or even yellow tongue if warranted).

The first type could be called "hairy", if "hairy" has to be used in description at all, but it is not necessarily "black" because it is "hairy".

A plea is made not to call all tongues with "staining", "black hairy tongue", because the staining is dark: they may or may not be hairy and they may or may not be "black". But this writer feels that the important thing to remember is that the condition could present as a "white lesion" and as such is included here.

G. GEOGRAPHIC TONGUE

(Syn. Benign Migratory Glossitis; Wandering rash of the Tongue; Glossitis Areata Exfoliativa; Glossitis Areata Migrans; Erythema Migrans.)

The writer includes this condition in this review of oral white lesions, feeling that benign migratory glossitis is not a white lesion, but that it could be mistaken for one: in other words, it is felt that

the condition could be an "indirect" white lesion, a mistaken white lesion because of contrast, due to comparison of surrounding tissues with a true erythematous lesion (which it really is). It occurs on tissues, mainly the tongue, which are normally (or perhaps at occurrence time a little abnormally) creamy-white. The lesion is the erythema, not the apparently whitish mucosa or filiform papillated surface.

Reference to geographic tongue as a white lesion has been made in the literature (Bhaskar, 1961), as follows in summary; "Lesions are irregular red patches of desquamation which heal on one side and extend on the other; however, surrounding area of the tongue appears white - partly due to contrast and partly because of elongation of filiform papillae; allergic reactions on tongue may give rise to similar lesions."

The author feels that the elongation of the papillae is only comparative, as the papillae on the area(s) of actual involvement have desquamated.

The clinical appearance is one of smooth, bright red areas, more marked at the edges, surrounded by an elevated, greyish-white border. The junction of several borders, which also are inclined to expand at times, produces a map-like appearance, thus accounting for the name "Geographic Tongue" when situated on this organ. It is usually found upon the dorsum of the tongue but can be seen ventrally or on the borders. There may be only one small lesion, or the whole tongue surface may be involved, even causing denudation. However, in

large or wide involvements, a serpigenous arrangement of the border may traverse large areas of tongue.

Almost daily changes of location of the lesions may be observed (Areata Migrans) or the lesion(s) may remain static for a long period. For this latter state, McCarthy and Shklar suggested the term "Glossitis Areata Persistans": although this writer has reviewed reports of oral cases occurring other than on the tongue (Cooke, 1962; McCarthy and Shklar, 1964).

Halperin et al (1953) reported the incidence as 1.4 per cent of all patients examined, the male to female ratio of affected patients being 1 : 2, occurring at any age. It is a benign condition and no treatment is needed. The cause is unknown. However, soothing of denuded areas is indicated as necessary and avoidance of any possible irritant.

The important factor in this section is undoubtedly differential diagnosis from white lesions, the main two being lichen planus and hyperkeratosis, the changing pattern of erythema migrans being diagnostic (if it occurs). Of course, biopsy is always called for in the case of hyperkeratosis which persists and biopsy will aid also in the diagnosis of lichen planus. (See under separate chapters).

References: McCarthy and Shklar (1964); Orban and Wentz (1960); Burket (1961); Thoma and Goldman (1960); Shafer, Hine and Levy (1963); Bhaskar (1961); Colby et al (1961); Cooke (1962); Halperin et al (1953).

H. ATROPHIC SENILE GINGIVITIS

Syn. Post-menopausal Gingivitis.

1. Clinical Manifestations.

Richman and Abarbanel (1943) found atrophic changes in the mouths of post-menopausal women, which changes objectively they described as pale and anaemic-looking gingivae, with sometimes grey-white streaks or patchy areas, or with whitish patches diffusely scattered. Also a whitish adherent film may be noted in some areas. Subjectively and concomitantly with these changes, a sensation of dryness or flatness of taste or burning sensation may be observed by the patient. Gingival bleeding may be noticed in some areas. This usually occurs, if occurrence takes place at all, no sooner than 6 months after menopause begins; it is not a common finding. Blake and Trott (1962) also found a number of patients show atrophic changes in the gingivae following the menopause, and they described the same symptoms stated above, their case also showing areas of hyperkeratosis appearing in patches or streaks. Colby et al (1961) confirmed the occurrence of such a condition, too. The interesting fact is that Blake and Trott also said that the condition appears not sooner than six (6) months after menopause whether natural, or surgically induced. The lesions appear in both edentulous and dentulous mouths, Colby et al stating that if the teeth are present, there is usually an associated gingival recession.

Glickman (1958) felt the condition could occur during the menopause as well as afterwards, but he, too, felt the condition was uncommon. He drew a comparison between the clinical appearance of senile atrophic

gingivitis and desquamative gingivitis, both conditions, he said, being due to a diminution in estrogen or else a disturbance in its utilisation. Massler (1956) outlined the following symptoms in some patients, associated with the menopause:-

1. A burning sensation in the tongue, the buccal mucosae and in the region of the pillars of the fauces.
2. Gross changes in the tongue, similar to those in Vitamin B deficiency.
3. An abnormal taste sensation described as "salty", "peppery" or "sour".
4. Diffuse erythema of the oral mucosa associated with a diffuse, painful, burning sensation.
5. Aphthous lesions before or after menstruation in the early stages of menopause.
6. Discomfort with and inability to wear, even well-fitting dentures.

The diffuse erythema appearance outlined in "4" above, would be due to an atrophic mucous membrane without keratosis.

Thoma and Robinson (1960) described the disease as characterised by hyperkeratinisation and areas of desquamation in the gingivae of older women, usually over 65 years of age. The subjective symptoms they also confirmed, as did Miller (1950) and others.

2. <u>Histopathology</u>.

Blake and Trott described the condition under the microscope as showing atrophy of the epithelium without complete loss of keratinisation, comparable with post menopausal changes in the vaginal epithelium. As

the condition progresses, keratinisation can increase and there may be greater prickle cell proliferation with a well-marked keratosis. Thoma and Robinson also found this. Richman and Abarbanel also described mucosal "stages" in the condition, the first consisting of atrophy of the germinal layer in general and of the prickle cells in particular. Secondly, with time and through any irritation, the stratum corneum, under abnormal growth stimulus, may become the site of hyperkeratosis.

Papic and Glickman (1950), followed by Montgomery (1951), confirmed through smear technique of exfoliative cytology that, whereas the menstrual cycle had no relationship to gingival keratinisation exhibited by different patients at specific phases of the cycle, a notable trend towards diminished keratinisation in the menopausal period represented a late phase of a physiologic tendency towards diminished keratinisation occurring with "ageing". They did warn, however, that gingival biopsy could disprove this. Wentz et al, however, in 1952 found that epithelial cells showed no significant changes with age and that hornification was characteristic for all ages. This was done by methods of biopsy, which also revealed a definite change, with advancing age, in the connective tissue corium, cellular elements being decreased and the fibrous intercellular substance increased and becoming coarsely textured. As Papic and Glickman, and Montgomery had pointed out, their statement that biopsy could disprove the fact that there is diminished keratinisation with age, had come true, or so it seemed.

It appears to the writer, however, that this is not a contradiction

- what has not been shown either by biopsy or by cytologic smear examination is the rate at which the processes are taking place: each test only shows the status quo for that particular time (i.e. the keratin shedding rate in older people may be, say, slowed due to general lessening of tissue activity, and in smears, fewer keratin cells would thus appear at any particular time).

Iusem (1950) had also found a correlation between vaginal smears and oral smears, in certain areas, during menstruation and that the distribution and maturity of mucosal cells are influenced by estrogen levels.

3. Aetiology

Orban et al (1958) said that the causes of an "atrophy" need not all be pathologic. Geriatric atrophy, or so-called senile atrophy, can be considered, at least in part, as a physiologic process. Starvation, disuse, excessive pressure and toxic influences might all lead to atrophy of an organ. In the final analysis, most atrophies, they said, are due to changes in cellular nutrition and metabolism.

Ziskin (1939) had concluded that hormones ("sex" type) exert a beneficial therapeutic influence on the gingivae and oral mucous membranes, and the writer infers a hormonal cause from this, an aetiology which has been stated by all writings on the subject which have been reviewed by him.

4 Therapy

Thoma and Robinson "controlled" cases of atrophic senile gingivitis by the topical application of corticosteroids. Goldman et al (1960), in recommending Stilboestrol in therapy, reported one very

good result of its systemic use. Blake and Trott also felt that hormonal therapy is beneficial, whereas Colby et al felt that its use is of questionable value.

Ziskin et al (1936) and Ziskin (1939) advised that so-called "sex hormones" may be employed successfully as an adjunct to local methods in some cases, but that they do not replace local methods of treatment, not, of course, including topical use of the sex hormones themselves, where applicable. They had seen no deleterious reactions, but recommended that therapy of this kind be undertaken by an expert in the field.

Richman and Abarbanel later pointed out that the terms "male" and "female" sex hormones should be abandoned, as the hormones display bi-sexual activities. It is an interesting point here that Burket (1961) said that atrophic senile gingivitis is not confined to women and he also stated that patients may have symptoms similar to those of desquamative gingivitis. Massler (1951) found that 60 per cent of sufferers responded satisfactorily to dietary corrections and vitamin supplements, and 35 per cent responded to estrogen therapy.

Richman and Abarbanel reported that the management of senile atrophic gingivitis with estradiol dipropionate administered by injection under the muco-buccal fold was found to yield most satisfactory results. In a few patients, gingival recession seemed to be decreased and hot flushes ceased.- (During treatment, diet was carefully watched and where doubt existed as to its adequacy, large doses of Vitamin B group, A and D were given.) The drug itself was

dissolved (1 mgm.) in sesame oil and given once or twice per week at first, thence once every 2 to 3 weeks. Nightly massage with an ointment base containing estradiol helped to maintain progressive improvement. Other sex hormone derivatives were not as efficient as estradiol dipropionate, but did bring about marked improvements also, which were:-

1. The normal pink colour of the mucosa returned.
2. The burning and dryness disappeared, while an increase in salivation was noted and any gingival bleeding was rectified.

Histologically, this therapy resulted in a physiological hyperplasia of the prickle cells, increased activity of the basal cells and, in some cases, even keratinisation of the stratum corneum. At no time was hyperkeratosis induced by administration of these estrogens. In fact, in a few instances, hyperkeratotic areas already present seemed to reduce in size.

5. <u>Chronic Desquamative Gingivitis</u>.

In an excellent review of the literature on the subject of chronic desquamative gingivitis, McCarthy and Shklar (1964) said that "it is evident that little agreement exists as to the cause of this condition, its therapy, or its basic nature." They added that there is doubt as to whether this condition is a specific entity, thus agreeing in the main with Burket (as previously stated) and Glickman. They felt that the lesions of post menopausal or chronic atrophic gingivitis resemble, to some extent, those of chronic desquamative gingivitis and they quoted Sognnaes et al (1956) who studied a case of desquamative stomatitis in a seventy one (71) years old woman by means of electron

microscopy and histochemistry. The disease had been resistant to hormonal, nutritional, antibiotic and surgical therapy over a ten (10) year period. Observations suggested that one of the important changes was the retention of immature basal-type epithelial cells throughout the thickness of the epithelium. Near the surface, the epithelial cells appeared to come apart readily as the result of a disintegration of the bond between the cell membranes. This certainly suggests to this writer an atrophic state. Later, McCarthy and Shklar pointed out the occurrence of desquamative gingivitis "associated" with mucous membrane pemphigus and lichen planus, pemphigus vulgaris, irritation and also a further type of desquamative gingivitis idiopathic in origin. It can also occur associated with various forms of specific chronic infections caused by bacterial and mycotic organisms, such as tuberculosis, moniliasis and histoplasmosis. They were attempting to prove that chronic desquamative gingivitis (or gingivosis, as it is often called) is not a specific entity and this is what they believe to be the position. However, they did state that desquamative gingivitis is <u>degenerative</u> in nature - it certainly is always associated with a chronic type, intense inflammatory infiltration of the corium leading to desquamation of epithelium, and some post-menopausal gingivitis is situated within this category. However atrophic senile gingivitis is, as the name clearly states, not "degenerative", but "atrophic", an academic point perhaps, but the writer fells that it is an entity; uncommon - yes, but nevertheless apparent. It is felt that the "senile" condition is really chronic, whereas desquamative gingivitis can be

sub-acute and is often a very painful condition. Subjective symptoms in atrophic senile gingivitis are not usually those of pain, although in post-menopausal gingivitis, which most seem to feel is synonymous with the "senile" condition, there can be a "burning" pain as stated by both Glickman and Massler; in fact most authors on the subject attest to this.

Perhaps the condition of change is manifested according to the degree of hormonal alteration and until such time as there is a clarification of the subject, the writer fells that the term "senile atrophic gingivitis" should be retained.

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