DIABETES MELLITUS

AND

ORAL DISEASE

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"...'you are mad; your great learning is turning you mad'. But (he) said, 'I am not mad .... but I am speaking the sober truth'."

The Acts ch.26:24-25 (R.S.V.)

The encouragement, help, patience and wisdom of family, friends and Faculty is hereby gratefully acknowledged.
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ABSTRACT

The purpose of this paper is to present an up to date review of the present knowledge of diabetes mellitus as it affects the oral cavity and associated structures, and to clarify some of the controversial aspects of the oral manifestations.

Diabetes mellitus is a public health problem which comes within the scope of dentistry as regards its detection, diagnosis, and treatment of its associated oral manifestations. Basically an endocrine-associated disturbance of carbohydrate metabolism, its aetiology is primarily hereditary but the overt disease may be precipitated by stress, infection or trauma in a susceptible patient.

The general physical signs and symptoms are discussed and its association with cardiovascular complications and skin and mucosal lesions such as lichen planus are dealt with. Recent studies on the role of insulin and its sites of action or impairment of action bear on the oral lesions and there is an association between the diabetic state and deficiencies of such substances as Vitamin C and Vitamin B complex.
An outline is given of urine and blood testing procedures and interpretation of these findings, particularly glucose tolerance testing. The detailed relationship of blood sugar levels to oral findings such as alveolar resorption, gingival tenderness, dry and burning mouth, and tooth mobility is discussed along with theories as to the modus operandi in bringing about the observed changes. There appears to be a definite increased incidence of periodontal disease in patients with decreased glucose tolerance. Dental caries appears to have an increased incidence in adult diabetics due to dietary factors and changes in the composition of saliva.

The nature of the changes observed in the dental and oral tissues are probably brought about by alterations in their nutritional state, protein imbalance, and impairment of antibody mechanism. There is clear evidence in diabetic mouths of lowered resistance in infection.

Animal and human biopsy studies using light and electron microscope techniques show non specific, but nevertheless definite pathological changes, particularly in the
vascular structures of the periodontal tissues. It is suggested that the thickening observed in the blood vessels impedes nutrition and elimination of waste metabolites. Insulin itself has been shown to promote bone resorption and increase the plasma calcium levels in experimental animals.

Treatment of the diabetic patient is aimed at eliminating periodontal and apical infection, if necessary under antibiotic cover, as atraumatically as possible. Guidelines are suggested for the preoperative and postoperative management of the diabetic and selection of anaesthesia.

References which have not been available for personal investigation and which have been cited from other reports are suitably marked (*).
CHAPTER I

DEFINABLE CONCEPTS OF DIABETES

Diabetes mellitus is a disease that cannot be precisely defined but which is characterised by a derangement of carbohydrate metabolism. It is a constitutional disease, the importance of which lies in the many complications which may ensue. Few diabetics nowadays die from the condition itself provided treatment is commenced early, but the complications still pose a world-wide public health problem.

It is defined by Marble as

"a chronic, hereditary disease characterised by an abnormally high level of glucose in the blood and the excretion of that sugar in the urine. The basic defect is an absolute or relative lack of insulin which leads to abnormalities of metabolism, not only of carbohydrate, but also of protein and fat".

This same authority states that diabetes is not a specific disease entity, but rather a multifaceted syndrome. Because of the high frequency of associated angiopathy, some authorities hold that this process is an integral part of the overall inherited disorder and that its time of appearance and extent are not directly related to the
existence or degree of control of the metabolic defect (vide infra. Oral Histopathology).

The main oral features we are considering in this paper are in patients suffering from the hereditary, idiopathic, or essential type of diabetes mellitus. This type may be further subdivided into

A. Growth onset (juvenile) diabetes.
B. Maturity onset (adult) diabetes.

"Juvenile" diabetes does not necessarily mean a type of disease which begins in childhood, although characteristically it appears during these years. This type is an abruptly beginning, aggressive type of disease, often first recognised when the patient is in a diabetic coma. The patients are prone to ketoacidosis, quickly lose the ability to produce their own pancreatic insulin, and do not respond successfully to oral administration of hypoglycaemic agents such as sulphonylureas. They are usually dependent on some form of insulin injection and the term "brittle" or "unstable" diabetes is often applied to the condition.

The "maturity onset" type usually appears in middle-aged
or elderly patients who are often obese and in whom the hyperglycaemia can be controlled by diet and/or oral hypoglycaemic drugs. In most cases the pancreas retains at least some ability to produce endogenous insulin, and it is not difficult to stabilise the patient's blood sugar level over a protracted period of time. The stages of the disease are
1. Prediabetes.
2. Chemical diabetes.

By way of definition it should be explained that "prediabetes" or the "prediabetic state" is that period of time wherein there is a loss of normal carbohydrate tolerance, without the signs or symptoms of overt diabetes. (Zarowitz). ²

Marble ¹ defines it as not a diagnostic label, but rather a concept or designation for the condition of persons having a strong hereditary predisposition for diabetes, but in whom at the time of study, all usual tests of carbohydrate tolerance yield results within normal limits.
Baird\textsuperscript{3} elaborated a special dental examination and scoring method and in a series of cases, in which he stated there was no characteristic dental pathology of diabetes, he referred to eight case histories in which there were "flat" sugar curves\textsuperscript{4,5,6} and expressed the opinion that there was an entity "prodromal diabetes" or "prediabetes" possibly caused by a hyperactive and excitable autonomic nervous system.

"Chemical diabetes" is a true diabetic state and is defined as a state in which symptoms are lacking and fasting blood glucose is within the commonly accepted normal range, but a glucose tolerance test yields abnormal values.

"Overt diabetes" usually follows on from "chemical diabetes" and is the condition in which blood glucose is higher than normal both in the fasting state and when determined at random, and where mild or severe diabetic symptoms are present.

These stages are summarised in the following table (from Marble)
<table>
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<th>Fasting Blood Glucose</th>
<th>Results of Glucose Tolerance Tests</th>
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<tr>
<td>Prediabetes</td>
<td>Absent</td>
<td>Normal</td>
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<tr>
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<td>Absent</td>
<td>Normal</td>
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<td>Latent Chemical</td>
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<tr>
<td>Chemical</td>
<td>Absent</td>
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<tr>
<td>Overt</td>
<td>Present</td>
<td>Abnormal</td>
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CHAPTER II

AETIOLOGY OF DIABETES

The aetiology of diabetes is obscure, but it has been shown that in certain cases a decrease in production of pancreatic insulin or an overproduction of the diabetogenic hormones from the anterior lobe of the pituitary are of paramount importance. However, in all diabetics there is an insufficiency of effective insulin in relation to the needs of the organism, although the actual secretion may be normal or increased.

Houssay and Biasotti investigated the relationship between the pituitary gland and carbohydrate metabolism and showed that the anterior pituitary acted in a "monitoring" type of role in this respect. Animals which had been rendered diabetic by pancreatectomy were subjected to hypophysectomy, and in these animals, carbohydrate metabolism, although unstable, approximated the normal and many of them survived for considerable periods.

Subsequent subcutaneous implantation of mammalian anterior pituitary tissue caused the animals to again produce typical diabetic symptoms, sometimes in an intense
form. Later investigations by Houssay\textsuperscript{13,14} substantiated these findings.

The significance of this work appears to lie in the fact that despite the absence of insulin in these animals, removal of the anterior pituitary brought about a degree of normality regarding carbohydrate metabolism, and furthermore, the experiments appear to demonstrate that the secretions from the pituitary are antagonistic to insulin or exert an inhibitory action on the pancreas, thereby affecting the secretions of the \( \beta \)-cells. In other words, it appears possible that an imbalance between the pancreatic and pituitary secretions may be responsible for the development of diabetes mellitus.

Later work done by Young\textsuperscript{15,16} and Long and Lukens\textsuperscript{17} could support such a conclusion. Long and Lukens showed that adrenalectomy and hypophysectomy produced experimental diabetes in the cat whilst Young was able, experimentally, to produce a transient diabetes in dogs by injecting them with fresh anterior pituitary extracts from an ox. By an increase in the dosage administered he produced permanent diabetes in five out of six of these animals. Subsequent histological investigations of the pancreatic tissues of rats, rabbits and dogs, all of which had been
rendered diabetic in the manner described, revealed that in these cases there were actual degenerative changes in the \( \beta \)-cells of the pancreatic islets.

Other theories which have been advanced for the etiology of diabetes are that it may be caused by primary liver disease and consequent upset in its glycogenetic function (Grusin)\(^{18}\), and that there are protein-like substances which "bind" insulin and thus oppose its action. (Antoniades, et al)\(^{20}\). Another theory suggested is that the problem is not in the "binding" of insulin, but rather an insensitivity to insulin at the cellular level. There is probably a link between this idea and the recently reported work of Cuatrecasas\(^{21,22,23}\). The logical flow-on from this concept is that the pancreas is stimulated to produce more and more insulin in an attempt to overcome the antagonistic forces and maintain normal metabolism. This can be done successfully for a long time but eventually the insulin mechanism suffers and the ability of the pancreas to produce insulin wanes, ("overwork hypothesis") the reverse of the effect on the adrenal cortex in patients taking prolonged corticosteroids. In the end diabetes becomes a disease of the pancreas, most prominently in patients with the aggressive type of the disorder in whom
the onset of the disease characteristically takes place in early life. (Marble)\textsuperscript{1}

For other theories of the etiology the reader is referred to standard authoritative texts on the subject.

Regarding predisposing causes, Joslin\textsuperscript{24} and many subsequent workers have placed much emphasis on an inherited tendency as the predominating inciting cause. This tendency is attributed to a Mendelian autosomal recessive character (Pincus and White)\textsuperscript{25}. Obesity, lack of exercise, luxury living are also reasons assigned for the increasing prevalence of the disease. (Rosenau)\textsuperscript{26}. Sindoni\textsuperscript{27} quotes 40 per cent to 80 per cent of persons with diabetes as being originally overweight, and remarks that whilst the overeating per se is not to be considered a potent factor, it should be realized that insulin stimulates appetite and perhaps such plethoric individuals over a long period of overeating may "exhaust" the insulin producing $\beta$-cells in the islets of Langerhans and develop diabetes.

Sweeney\textsuperscript{28} and Selye\textsuperscript{29} are amongst investigators who
incriminate severe physical, mental and emotional strain as precipitating factors in causing the disease in those patients in whom a predisposition exists.

The following table (after Marble) shows the Varying Degrees of Probability for the Later Development of Diabetes.

1. Identical twin of a diabetic.
2. Persons with diabetes in close relatives (theoretically 100% probability when both parents are diabetic).
3. Women with abnormal obstetrical history.
   a. Tendency to large babies (10 lb. (4.5 Kg.) or more).
   b. High perinatal mortality.
   c. Repeated miscarriages.
   d. Toxaemia of pregnancy.
4. Obese individuals.
5. Persons with diabetes-like vascular and neurologic manifestations.
REFERENCES: CHAPTER II


CHAPTER III.

DIABETIC SIGNS, SYMPTOMS AND COMPLICATIONS - GENERAL

It is possible, but unlikely, that a dental surgeon will perceive the primary classical symptoms of diabetes in the course of a chairside encounter. Being a disease of insidious onset, symptoms are often absent in the early stages, and the onset is often of such a gradual nature that the patient may be unaware of their presence. The common presenting symptoms of diabetes are frequent micturition (polyuria), increased thirst (polydipsia), increased appetite (polyphagia) and pruritus confined in the main to the genitalia. The genital lesions are usually associated with Candida albicans and usually present a markedly red base with circumferential vesicopustules present. The condition is said to occur in 50% of diabetic women. (Pastras and Beerman)\textsuperscript{34}. Loss of weight in spite of the increased appetite and lassitude are less common early symptoms, as are also drowsiness, leg cramps, and lowered general resistance to infections such as boils, paronychia and traumatic injuries such as cuts and abrasions.

The classical statement occurs in numerous articles in
the literature that a diabetic has a "fruity odour" or "acetone odour" to the breath, and presupposes a well-worn olfactory pathway possessed by a profession whose daily diagnoses are made in the atmosphere of patient exhalations, and if in fact it is discerned, it usually indicates an advanced stage of ketoacidosis.

Whilst the chief signs of the disease are glycosuria and hyperglycaemia (vide. Diagnosis) these may obviously be elicited only by testing. Strong and Baird\textsuperscript{30} remark that cases without complications will usually show no abnormal physical signs attributable to diabetes.

The complications of their disease to which diabetics are prone include ketosis which may lead to coma and death, arteriosclerosis and other generalized cardiovascular conditions which are a frequent cause of circulatory disorders of the extremities, ocular complications, the most common of which are retinitis, cataract formations and atrophy of the optic nerve, and peripheral neuritis.

Infectious diseases, such as pulmonary tuberculosis, formerly had an increased mortality when associated with
diabetes. As recently as 1950 to 1960, Blum and Atagun\textsuperscript{31} reported a death rate of 26.6\% in tuberculous diabetics treated in a large city hospital as against 19.9\% in the non-diabetic group. A decreasing percentage of incidence is quoted by the Joslin Clinic, where Younger and Hadley\textsuperscript{32} give an overall figure of deaths from tuberculosis in diabetics as 5.5\% in the 1920's, 3.4\% in the early 1930's, 0.7\% in the early 1950's, 0.3\% from 1956 to 1965 and no deaths from 1965 to 1968. As a general statement, however, infections of all kinds tend to be more severe in the presence of diabetes, (vide infra.) no matter in what area of the body they may occur.

The skin is a not unimportant and reasonably accessible area in which the dental surgeon can observe the manifestations of diabetes. Long standing cases may frequently manifest a sallow pigmentation of the skin known as carotenemia or xanthosis (xanthochromia), usually associated with an increased carotene and cholesterol blood level. It is the result of liver dysfunction and the inability of the liver to convert carotene, as the ingested vegetable pigment, to vitamin A in the liver. An area where it may be observed during a dental examination is the naso-labial fold.
Probably the most significant skin condition is *necrobiosis lipoidica diabeticorum*, a condition which is stated by Muller and Winkelmann\(^3\) to be almost certainly a precursor of the diabetic state. The lesions comprise oval, firm yellowish plaques, with a scaly sclerodermoid appearance, with a predilection for location on the anterior surfaces of the legs and feet. A patient with such lesions should be given periodic cortisone-glucose tolerance tests to confirm the diagnosis of diabetes or otherwise. The possible connection between *necrobiosis lipoidica diabeticorum* and *lichen planus* has been noted (Jolly)\(^4\).
REFERENCES: CHAPTER III


CHAPTER IV

EPIDEMIOLOGY OF DIABETES

The detection and control of diabetes is a world-wide and annually increasing public health problem in which the dental profession should play an important part. The number of known diabetic patients and the number of individuals with undiagnosed diabetes who may seek dental treatment are greater than the average dental practitioner realises. Burket and Sindoni state that for every four known cases of diabetes, there exist three undetected, whilst Cheraskin gives a figure of one known established case to four undetected or prediabetic persons, with an overall diabetic incidence of 1 in 160 of population of the U.S.\textsuperscript{35,36,37,47.}

The prevalence and incidence of the disease along with the methodology of the sampling procedures, are documented in authoritative works on the subject\textsuperscript{38} and studies have reported on the incidence of periodontal disease, caries and other oral conditions in association with diabetes\textsuperscript{39,40,41,41a.}
Public health studies in the U.S. conducted by Wilkerson \(^{42,47,43,44}\) disclosed that in 1953 diabetes was eighth highest on the list of causes of death, and in a projection of the latest statistical evidence available, it was estimated that within twenty years it would move up to third place as a cause of death, mostly as a result of associated cardiovascular complications \(^{27,45}\).

Despite mass screening programmes in various countries, the incidence of diabetes continues to rise, and based on World Health Organisation figures there will still be millions of diabetics yet to be found by the time world population reaches 7.4 billion about the year 2000, particularly bearing in mind that diabetics appear to increase at twice the rate of the total population \(^{46}\).

Despite what may be said in the literature and elsewhere in this paper as to factors such as emotional stress, trauma, obesity, and infection playing a part in bringing about a diabetic state, it seems clear that hereditary factors are the most important in the onset of the condition, and control of the disease on a world-wide scale would of necessity involve drastic curtailment of the reproductive activities of the existing world diabetic population.
REFERENCES: CHAPTER IV


CHAPTER V

PATHOLOGY OF DIABETES AND ROLE OF INSULIN

A brief account of the biochemistry, physiology and pathology of diabetes is necessary for a grasp of the fundamental concepts of the disease and this section is a summary of the more recent publications on the subject.

In the process of digestion of carbohydrates they are normally reduced by enzymatic action to monosaccharides in the small intestine, and these monosaccharides are transferred via the portal circulation to the liver, where they are stored as glycogen. Some of the monosaccharides in the form of glucose pass subsequently to the systemic circulation and are partly stored in muscles and tissues, also in the form of glycogen.

In the process of enzymatic digestion of proteins, the end products are amino acids which are likewise conveyed to the liver.

The fats are hydrolysed into fatty acids and glycerol by the lipases, or fat-splitting enzymes, and the bile salts.
In their passage through the intestinal wall they are resynthesised, some to neutral fat, and some to phospholipides, and as such enter the lymphatic system to reach the blood stream via the thoracic duct. Normally the liver is capable of converting some of this digested protein and fat into glucose.

One of the overall "monitoring" factors in the above processes is insulin, a protein made up of two chains of amino-acids joined together by disulphide linkages, which is secreted by the $\beta$-cells of the islets of Langerhans in the pancreas. Histologically, specific granules may be demonstrated in the $\beta$-cells, and it is generally accepted that they represent stored insulin or a pro-insulin stage.\(^{48,49}\). In diabetic cases of all types investigators have failed to show a consistent histopathological pattern of change in these cells, although hydropic degeneration, disappearance of the granules, and cellular proliferation resulting in hyalinization of the islets have been reported\(^{50}\).

However, this is not the whole picture, and work done by Maclean and Ogilvie\(^{51}\) and Ogilvie\(^{52}\) showed that when quantitative measurements were made of the $\beta$-cells and their
relative and absolute mass within the pancreas, a marked diminution of this tissue was found in nearly all instances of diabetes, along with abnormal histological β-cell features.

These abnormal cases correspond to work on experimental animals (q.v. this paper) where the β-cells are rendered inactive by drugs, whereas the cases in which no quantitative or histopathological abnormality is observed resemble the early stages of that type of experimental diabetes in which signs of hyperactivity of the islets suggest an increased demand for, rather than a lack of insulin. The two extremes may be best summarised by the statement that

"the notion best applicable to all cases of human diabetes is still that of a lack of metabolically effective insulin as the major endocrine defect in man ..."

It is clear that up to the present, the existence of absolute or relative insulin deficiency cannot be proved or disproved to be due to either a pancreatic or extrapancreatic process - in other words on available evidence we just don't know, but it is equally clear that the hyperglycaemia of insulin deficiency is a consequence of the underutilization and/or overproduction
of glucose. The three cardinal features of insulin deficiency are listed by Goodman and Gilman\textsuperscript{54} as 

1. In the absence of insulin there is a marked reduction in the rate of transport of glucose across certain cell membranes.

2. In the absence of insulin there is a marked reduction in the activity of the enzyme system that catalyses the conversion of glucose to glycogen.

3. In the absence of insulin there is an abnormally high rate of conversion of protein to glucose.

It is important in the light of the observed clinical pathology in the mouths of diabetics to realise the areas in which the pathogenesis of absolute or relative insulin deficiency may operate. These are listed by Stauffacher and Renold\textsuperscript{53} as

Area 1. Defective insulin synthesis from amino-acids.

- Impairment of pro-insulin cleavage.
- Impairment of granule dissolution.

Area 2. Impairment of penetration of insulin through \(\beta\)-cell plasma membrane.

Area 3. Thickening of \(\beta\)-cell basement membrane.

Area 4. Thickening of pancreatic capillary membrane.
Area 5. Impairment of diffusion of insulin in pancreatic intercellular space.

Area 6. Impairment of penetration of insulin through pancreatic capillary endothelium.

Area 7. Modification or destruction of circulating insulin.

Area 8. Impairment of penetration of insulin through peripheral capillaries.

Area 9. Impairment of penetration of tissue cell basement membranes.

Area 10. Unresponsiveness of peripheral target cells to insulin action.

A clear understanding of the above areas of action is essential to the interpretation of the findings reported later in this paper of the breakdown of oral structures in the mouths of diabetics where there appear to be no local factors such as irritation to account for the oral lesions. Furthermore, it would be expected that the effects on oral lesions would fall into the Areas 7-10 above, in other words, cases of "relative insulin deficiency" in contrast to "absolute insulin deficiency" (Areas 1-7) where the hormone is either not being produced or its path of access to the blood stream is impaired.
Reverting to the metabolic pathways in diabetics, the ability of the liver and tissues to store glycogen is diminished, resulting in an excess of glucose in the blood, and, in addition, the conversion of protein and fats, especially the former, is increased. The derangement of carbohydrate metabolism also leads to a breakdown in the reduction of fats, which, instead of being oxidised to $\text{CO}_2$ and water, are only metabolised to an intermediate stage of aceto-acetic and beta-hydroxybutyric acids, giving rise to the complication of **ketosis**. At this stage, acetone bodies may be detected in the urine (vide Diagnosis). Glycerol, the other product of fat digestion, is converted to glucose and excreted as such in the urine.

We have, therefore, the paradoxical situation of a patient with too much blood sugar, yet continuing to convert protein and fat to more sugar. There is general agreement that it is the conversion of protein to sugar in diabetics which accounts for the loss in body weight and wasting. While the liver plays the most important part in carbohydrate metabolism, fundamentally insulin governs the blood sugar concentration, and, reciprocally, the latter governs insulin secretion.
In addition to the abnormally high rate of conversion of protein to glucose in the absence of insulin (see 3 above) there is also a reduced movement of amino-acids into muscle and possibly other cells, and reduced incorporation of amino-acids into protein. In insulin deficiency, amino-acids do enter the hepatic cell, where they are deaminated and oxidised to yield pyruvate, and contribute to the hepatic overproduction of glucose. (Extor, Jefferson, Butcher and Park)\textsuperscript{55} (Friedman, Goodman and Weinhouse)\textsuperscript{56}. Insulin deficiency also removes antagonistic control of protein catabolism from adreno-corticosteroids and thyroid hormones, thereby tilting the protein anabolic-catabolic balance towards catabolism.

The exact role of insulin action is still largely obscure, but there appears to be a recent breakthrough in the understanding of its role as a growth controlling agent in the work of Cuatrecasas\textsuperscript{21,22,23} who showed that it was required for proliferation and differentiation of cells, and whose effects are channelled through the twin cyclic nucleotide (cyclic AMP and cyclic GMP) system.

Another line of recent research has discovered that large
doses of vitamin C, given supplementary to insulin, reduce the insulin daily requirement. Daniel and Dice\textsuperscript{57} reported on a juvenile diabetic, stabilised on a daily dose of 32 units of insulin from age 16 whose insulin requirement was reduced by one unit daily over a period of days and supplemented with hourly doses of vitamin C. By titrating the vitamin C dosage against blood sugar, a normal blood sugar level was maintained with 13 units of insulin daily and 11 g. vitamin C. This research may well revolutionise the future treatment and prognosis for diabetics.
REFERENCES:  CHAPTER V


CHAPTER VI

DIABETIC TESTING PROCEDURES

The responsibility for the accurate testing and diagnosis of the diabetic belongs primarily to the patient's physician, but in view of the comparatively large percentage of unrecognised diabetes which may come routinely into the province of the dental profession, an understanding of testing procedures is mandatory, and the simple ones can well be carried out in the dental situation and any suspicious findings referred for medical evaluation\textsuperscript{37,58,59,60}.

The normal whole blood glucose values are quoted by Shafer, Hine and Levy\textsuperscript{61} at 60-90 mg. per cent, and serum glucose values in the range of 70-105 mg. per cent. Joslin's text quotes the United States Public Health Service standard as a fasting whole blood glucose level of 110 mg. per cent. Cheraskin and Ringsdorf\textsuperscript{62} and Ringsdorf Cheraskin and Hollis\textsuperscript{63} after extensive investigations of blood glucose levels, placed the normal whole blood glucose level for perfectly healthy subjects in the narrow range of 70-79 mg. per cent. Values above the upper limits of these ranges could well point to the
presence of diabetes, but values in the so-called normal range and in the presence of other suspicious oral and general signs and symptoms, would not preclude the possibility of the presence of the disease and may indicate further testing should be carried out.

Any spill-over of sugar in the urine above a concentration of 10-20 mg. per cent is suggestive of diabetes, as there is normally no sugar in the urine except in such stress situations as fever, hyperthyroidism, after general anaesthesia, and occasionally in rheumatoid arthritis patients, or others who are taking large doses of salicylates.

a. Urinalysis

1. Sugar in the urine may be qualitatively determined using Clinitest (Ames & Co.) tablets, which comprise anhydrous copper sulphate, anhydrous sodium hydroxide, citric acid and sodium bicarbonate. The tablet is dropped into a measured amount of diluted urine (say 10 drops urine and 20 drops water). After the reaction has subsided, if glucose is present, the colour change is green, yellow through red with increasing amounts of glucose. Testing should be done
two hours after a meal. Misleading results may occur in a true diabetic with a raised renal threshold of excretion or in a normal patient with a low renal threshold of excretion. 

Clinistix (Ames & Co.) is a paper strip impregnated with glucose oxidase and changes green, through blue to purple with glucose. It is specific for glucose, and is normally dipped in undiluted urine.

2. Ketone bodies may be detected using Acetest tablets or Ketostix strips (Ames & Co.) and give varying colour changes due to the reaction of urine with the sodium nitroprusside reagent. Urine with positive sugar plus ketone bodies is invariably diabetic.

3. Albumin (protein) in the urine may indicate renal involvement in diabetes and may be tested with Albustest tablets or Albustix strips (Ames & Co.). The degree of colour change is again compared with a colorimetric chart supplied.

b. Blood Glucose Determinations

The type of sample (capillary or venous) and the time of sample (fasting or post prandial) are the critical factors
in a blood glucose determination and "random sampling" can be a completely misleading procedure.

Capillary blood samples are the easiest to obtain, but after the intake of food may be 20 mg. to 50 mg. percent higher than venous blood within one to two hours. The usual procedure is to test in the fasting state (i.e. no food for twelve hours), but under these conditions many borderline cases may go undetected and the test procedure should be "tailor-made" according to the purpose of the information required. For example, in a patient taking a long-acting insulin compound once daily before breakfast, a fasting blood glucose determination would be useful to determine how much insulin should be prescribed, whereas a test taken two to three hours after a meal could be of more use in diagnosing a "mild" case or alternatively to give an indication, if the patient was diabetic, how much intermediate or rapid acting insulin would be required to balance the remainder of the day's requirements.

Modern methods favour the use of plasma rather than whole blood for these determinations, as anaemias and polycythaemias, if present, appear to alter the true
value of the extracellular glucose. The values of plasma or serum glucose are approximately 15% higher than for whole blood.

For a quick semi-quantitative determination, a drop of blood is placed on a Dextrostix strip (Ames & Co.) for exactly one minute, the excess blood is washed off, and the colour change compared with a graduated colorimetric scale on the side of the Dextrostix bottle, which gives a break-up into glucose levels of between 40 mg. to 250 mg. per 100 ml. Dextrostix, like Clinistix, are impregnated with glucose oxidase as the reagent.

c. Other Chairside Tests

The above method of capillary blood testing can be done quite conveniently at the chairside.

Kupfer also suggests using the same technique after extractions, that is, dipping a Dextrostix strip in the socket taking care not to get it contaminated with saliva. In a test applied to 119 patients, he found 24 which showed blood glucose values above 130 mg. per cent. Of this group, four were known diabetics, and of the other twenty, eight also gave positive urinalysis tests.
Two of these were tested in the non-fasting state, but the other six who had positive urine were in the fasting state. This figure of approximately 5% incidence of undetected cases warrants consideration of the technique as a screening procedure, but it should be remembered that it is higher than the norm, which is 0.9% to 1% overall for unrecognised diabetics and a further 2.8% for potential diabetics.

An ingenious test modification was suggested by Truelove who obtained a high proportion of positive tests with Clinistix absorbing lacrimal fluid from the lower eyelid.

d. Glucose Tolerance Tests

The recognised laboratory method of determining a diagnosis of diabetes is by the standard oral glucose tolerance test. The patient to be tested has unrestricted diet for at least three days, provided the carbohydrate intake is at least 150 gm. to 250 gm., and is submitted to testing in the fasting state (twelve hours fast). A fasting determination of the blood sugar and urine is made and the patient given orally 100 gm. of glucose in the form usually of sweetened drink.
Samples of blood and urine are then taken at 30 min-60 min
120 min and 180 min intervals and the amount of sugar
determined to determine the patient's ability to deal
with the experimental load. There is much disagreement
as to what should be regarded as a normal sugar curve
but the following standard is acceptable\textsuperscript{5,6,37}.

i. Fasting blood glucose below 100 mg. per cent.
AND

ii. Level does not rise above 150 mg. per cent at
any time.

AND

iii. Blood glucose level returns below 100 mg. per
cent within 2 hours.

The so-called cortisone-primed glucose tolerance test, in
which the subject is given 50 mg. cortisone acetate
eight and a half hours and two hours before the standard
test dose, is said to increase the sensitivity of the
results, but may give a misleading picture.

The estrogen component of oral contraceptives has been
shown to decrease glucose tolerance, and should be omitted
for one cycle prior to a glucose tolerance test.

Approximately 85\% of women on the "pill" show this phenomenon
which is due to the estrogen potentiating the effect of
prednisolone in suppressing the plasma insulin response
to oral glucose\textsuperscript{66,67}. 
REFERENCES: CHAPTER VI


CHAPTER VII

DIABETIC TREATMENT

Treatment of diabetes mellitus is not a dental responsibility, but knowledge of the treatment and its effect on dental procedures is of prime concern. Lack of dentomedical liaison in this area will be disastrous for the patient and frustrating for the custodians of the patient's health.

Diabetes is controlled by
a. Diet.
b. Insulin - in various forms.
c. Oral hypoglycaemic agents.
d. Combination of one or more of the above.

Diet is the basic method of control and is the first step in maintaining carbohydrate balance and rectifying abnormal conditions such as obesity.

Insulin, in one of its forms, is usually prescribed in a.

a. Patients with diabetes whose onset is in childhood or adolescence.
b. Most patients with diabetes whose onset is before 40 years of age and older patients with an unstable ("brittle") form of the disease.

c. A small proportion of patients with maturity-onset type of diabetes.

d. Patients with ketoacidosis and/or coma.

e. Patients who have undergone surgery or who are suffering from febrile illnesses.

Preparations of insulin are quick-acting, intermediate-acting, and slow-acting, and 24 hour dosages vary from 10 to 100 units or more, and there are seven types of preparations available. There is no recorded contra-indication to the use of insulin with the normal therapeutic agents used in dental procedures.

The oral hypoglycaemic agents are in two groups.

a. Sulphonylureas
   i. Tolbutamide
   ii. Chlorpromamide
   iii. Acetohexamide
   iv. Tolazamide

and

b. Biguanides
   i. Phenformin
   ii. Metformin.
The sulphonylurea compounds act by stimulation of the β-cells of the pancreas, but the mechanism of action of the Biguanides is still obscure.

No reports exist in the literature of untoward effects during routine dental procedures with patients taking these compounds.
CHAPTER VIII

ORAL SYMPTOMATOLOGY IN DIABETES

a. General
From the earliest recorded observations up till the present time the oral manifestations or supposed manifestations of diabetes have evoked as much controversy as any other aspect of dentistry.

Surveying the picture historically, we can note that records of oral symptoms up to approximately 1922 or slightly later would be made on the mouths of uncontrolled diabetics, or at best, on patients who could be controlled with dietary restriction. Insulin (crystalline) was isolated by Banting and Best in 1921, and the more stable insulins were in use just before World War II.

Up to this time it could well be called the "Era of Generality", but during and after World War II more scientific method was applied to clinical observations and laboratory studies and up to approximately 1960 it could well be called the "Era of Rationality". Subsequent to this period the detail and nature of the studies could well bring us to the "Era of Specificality".
Investigations and reports of this period had the advantage of hindsight on a large volume of literature on diabetes and oral disease as well as the benefits of modern techniques of statistical, microscopic and biochemical analysis. Areas of incomplete reporting in previous studies were covered, and whilst many detailed aspects remained unresolved, research more specifically pin-pointed important conclusions in the study of the oral-diabetic syndrome of symptoms.

Magitot (1887) is quoted by Schour\(^69\) as first drawing attention to loosening of the teeth in patients suffering from diabetes but Rhein\(^70\) was the first investigator to use the term "diabetic gingivitis" to describe the marginal periodontal pathology in such cases. He also observed that there was bone loss in the diabetic state. Further general observations were made by Croftan\(^71\) who added descriptions of intense congestion, fungus growths, necrosis, pyogenic infections of the gums and gangrene to the clinical picture. Similarly, Williams\(^72\) described a high incidence of "pyorrhoea" in diabetics and Rosenthal\(^73\) states that a characteristic feature is rapid loosening of the teeth with acute onset of suppuration along both jaws. Schour\(^69\) also cites Biedl with a description of swollen and spongy gums which bleed easily, pocket
formation and suppuration which are associated with the hyperglycaemic condition, and Slanck, who noted that teeth which had become loose sometimes became firm again after care (presumably he means more adequate control) of the diabetes.

Taking an opposite view Eisner\textsuperscript{74} observes that whilst pyorrhea appears to be more prevalent in diabetics than in the normal population, diabetes is not necessarily associated with stomatitis, gingivitis, pyorrhea or rampant caries, likewise Badanes\textsuperscript{75} Beardwood\textsuperscript{76} and Aiguier\textsuperscript{77} agree.

Many workers have suggested biochemical analyses in the investigation of the systemic background in periodontal diseases, but Niles\textsuperscript{78} was the first to suggest there should be routine urine sugar examinations in all cases of alveolar resorption. Justification for this has been later amplified by others particularly the Alabama investigators (Sheridan, Cheraskin et al.)

Statistical or quantifying studies in this period of reporting in the literature are conspicuous by their infrequency. Zilz\textsuperscript{79} made a statistical study of 100 Viennese diabetics of which he states 71 suffered from
"paradentosis", and of these there was a higher occurrence in women than men. His figures show that in 25.3% the periodontal condition appeared simultaneously with the onset of diabetes, in 47.9% it appeared prior to the diabetes, and 9.8% it immediately followed the diabetes. This study embraced adult and juvenile patients, but in the 5 cases under 16 years old no periodontal pathology was reported.

Boenheim lists the cases of 14 investigators who examined a total of 1575 cases of periodontosis and found 225 (14.3%) cases of diabetes, which is a relatively small number compared with the reports of others. His comment is that "there is no close connection between diabetes and periodontitis".

As a further typical example of the "dragnet involvement" of oral lesions and diabetes in this era, Prinz and Greenbaum may be quoted. They list the following as pathognomonic of the diabetic state

"typical fruity odour, deep red and dry mucous membrane, burning sensation in the mouth, constant thirst, teeth coated with light yellow calcareous deposits, increased sensitivity of necks of teeth, circular caries, failures in amalgam restorations, chronic gingivitis, neuralgiform pain on both sides of face, enlarged tongue with imprints of teeth, enlargement of normal tongue tissues, mycotic stomatitis, trophic ulcers of the palate...."
Obviously there is very little oral pathology left to be incriminated in the diabetic state if these statements are to be accepted.

Whilst the observations recorded above may be taken at face value, they cannot be given undue scientific authority because of obvious defects in the compilation of data. For example, virtually no control studies are made in any instance, the terminology of the periodontal conditions is vague and non-standardized as are the descriptive terms, actual methods of the diabetic diagnosis and treatment are seldom mentioned, the samples are too small to draw definite conclusions and concomitant systemic pathology is not reported on or considered in the results. One histopathologic study is reported (Gescheff)\textsuperscript{82} and the conclusions are of doubtful validity.

Up to the outbreak of World War II the state of knowledge of oral conditions in the diabetic state presents a confused and controversial picture and it was left to later investigators, particularly those of more recent years who were able to use more sophisticated biochemical techniques and electron microscopy to rationalize studies of the condition. Furthermore it should be remembered that patients up to this period had their diabetes controlled,
(if it was controlled at all), by diet and insulin injection (Crystalline Insulin) alone. The more stable Protamine Zinc Insulin and Globin Zinc Insulin were developed in 1936 and 1939 respectively, the oral hypoglycaemic agents were discovered in 1956/57\(^3\), and the whole clinical picture could well be affected by the method and duration of prescribed treatment.

b. Dental Caries

In keeping with the general remarks on the soft tissues briefly outlined previously (Oral Symptomatology - a. General), early reports on the relationship between the diabetic state and caries were based on clinical intuition applied to the observed data.

Magitot\(^4\) stated that the teeth of diabetics were unusually prone to caries, and that the decay reduced them to "tooth stumps". Grunert\(^5\) observed rampant cervical decay in diabetics, with gingival recession, and remarked that when adults, formerly caries free, developed an increased susceptibility to caries, diabetes should be suspected.

Lederer\(^6\) studied the pH of diabetic saliva (158 cases), but found a predominance of alkaline saliva, whilst 85
cases had glucose in the saliva and 73 did not. He assumed, probably quite wrongly, that the higher caries incidence he observed was the result of acid produced by the fermentation of this glucose in the saliva.

An unusual slant is postulated by Misch. He states that caries progresses more rapidly in diabetics because there is a general derangement of body metabolism causing a disturbance of metabolism in the dentin, thus enabling caries to progress more rapidly once the enamel is penetrated.

A dissident voice is raised by Fleischmann who says caries susceptibility is no greater in the diabetic than in a normal person.

The above reports all appear in the literature in the pre-insulin period, where dietary management of the disease did not permit the intake of sugars or carbohydrates in appreciable amounts. The so-called "under-nutrition" treatment, prescribed, for a child, 25 gm. to 30 gm. protein and 170 gm. fat daily, and no refined carbohydrates. However the "opinion" prevailed that caries incidence was increased above normal.
Boyd and Drain et al.\textsuperscript{89,90,91,92,93} reported in various studies from 1928 through 1944 that in diabetics controlled with insulin and diet, there was an arrest of carious lesions and limited occurrence of new ones. The work principally dealt with the incidence of caries in younger age groups.

de Berry\textsuperscript{94} also made a detailed study of carious lesions in a group of young patients. This group, in addition to being on a very low refined carbohydrate diet, also had dietary supplements of cod liver oil and orange juice, and it is stated that there may be some positive relationship between the intake of cod liver oil and orange juice and the number of cavities occurring in the mouth. Also, a positive relationship was reported between the length of time the patients were on the prescribed diet and the number of cavities which developed. There was no relationship between the intake of insulin (i.e. the severity of the diabetes) and the number of cavities or the state of arrest of the carious lesions.

Kent\textsuperscript{95} who made a survey of one of the largest samples of diabetics (5000 cases) noted that diabetic children and adolescents up to age 20 years had teeth almost free of caries, but after 20 years the incidence markedly increased.
In Ziskin's et al. study\textsuperscript{96} no significant reduction or increase in caries was noted between diabetic and non-diabetic patients, and these investigators considered that their findings minimised the conclusions of Boyd and Drain that caries could be controlled by nutritional means via the general metabolism.

Cohen\textsuperscript{97} reported on a group of 27 juvenile diabetics between ages 6 to 30. Of these, eleven cases formed part of the previous study by Rudy and Cohen\textsuperscript{98,99}. Compared with a matched group of controls, the diabetic patients were found to have a greater incidence of caries after age 21. Only in one case was there a variation of increase in salivary glucose between diabetic and normal persons. Of the diabetics, those who indulged in dietary laxity and insulin dosage omissions, showed greatest increase in caries susceptibility.

In comparing Cohen's findings with Boyd and Drain's, the differences may be accounted for by firstly area (endemic) differences, (Cohen's patients were a New England group whereas Boyd and Drain's were located in Iowa), and in addition, Cohen's patients had radiographic surveys whereas Boyd and Drain's did not.
It is significant that in diabetes the salivary glands may be altered, and the physical or biochemical composition of the saliva varies from that of normal persons. This fact, and the parotid-pancreas relationship has been reported on by Flaum, Kenawy and Birnkrant, and obviously would bear on caries incidence.

An excellent modern summary-study by Mascola also makes a special point of the fact that with an increase in the blood sugar levels in diabetes, there is also an increase of the glucose content of the serous saliva of the parotid gland. He considers that this viscous fluid coupled with a soft diet may well cause an increase in caries in a debilitated oral environment in a diabetic, but that this fact has not been well documented and requires further study. Campbell showed that a significantly higher amount of glucose was present in the saliva of diabetics (0.44 mg. to 6.33 mg/100 ml.) than non-diabetics (0.24 mg. to 3.33 mg/100 ml.), but that there was no correlation between the blood sugar level and the saliva sugar level of any one patient.

C. Salivary Calculus

There are numerous references in various papers to salivary calculus formation in diabetic mouths (usually
reported in conjunction with other findings), one of the first being that of Kent\textsuperscript{95} whose group under 20 years of age showed a marked tendency to excessive soft yellow deposits of supra-gingival calculus. This phenomenon is allegedly due to the acidosis - a large amount of alkali is excreted through the urine along with a proportionately large amount of calcium through the saliva, thus causing excess calculus.

Mackenzie and Millard\textsuperscript{106} found increased prevalence of interproximal calculus in diabetics against non-diabetics was either small or non-existent, as did Benveniste, Bixler and Conneally\textsuperscript{107} who made detailed periodontal and other scores (Ramfjord's method) and found no significant differences in calculus formation between the two groups.

Other workers who used recognised scoring methods\textsuperscript{108,109} to assess calculus, oral debris etc. and who found no significant differences between diabetic and non-diabetic groups were Hove and Stallard\textsuperscript{110} and Cohen et al.\textsuperscript{111}. Campbell first reported\textsuperscript{105} higher calculus, periodontal and oral debris indices, but later\textsuperscript{40} reported that the only significant difference was a raised calculus index for the non-diabetic male as against the non-diabetic female. He agrees, however, that overall periodontal disease is greater in diabetics than non-diabetics.
d. Mucosal Lesions

Reports of soft tissue lesions in the mouths of diabetics have centred mainly round the gingival tissues and the periodontium and are dealt with elsewhere in this paper under the heading *(Periodontal and Bony Lesions).* However, it is of importance to note that the gingivae are frequently referred to in the literature as being marked by tenderness; or itching, and are linked with the symptoms of xerostomia (dry mouth) and stomatopyrosis (burning mouth) as the most common triad of oral symptoms found in the mouths of diabetics. These three symptoms have been the subject of exhaustive investigations as correlated with the glucose tolerance test for the patient, and are discussed in detail in this paper under the heading *(Glucose Tolerance Tests).*

Recent preliminary investigations by Jolly\(^4\) indicate there may be an association between lichen planus and the diabetic state. Of a consecutive series of 33 patients presenting with a certain diagnosis of oral lichen planus, 85% (28 cases) were found to have abnormal carbohydrate metabolism as determined by a 2-3 hour glucose tolerance test, as against a prevalence of 12% to 14% in the average population. The sugar curves followed a typical "diabetic" pattern with initial hyperglycaemia followed by delayed
hypoglycaemia and insulin release. Further 5 hour glucose tolerance tests and concurrent serum immunoreactive insulin determinations on 19 of the 28 patients showed two distinct patterns
1. Raised base level of glucose with delayed peak rise.
2. Raised base level of glucose with a "flat" glucose curve.

No breakup of the percentage of these two categories is given.

There are no reports in the literature which give any indication that there is a connection between the microstructure of oral lichen planus and the microscopic changes observed in the mucosa of diabetics (see Oral Vascular Pathology) but this may be an area of further useful study.

The connections between necrobiosis lipoidica diabeticorum and lichen planus is discussed elsewhere (Diabetic Signs Symptoms and Complications - General).

Angular Cheilitis is by no means always associated with the diabetic state, but it is usually an indication of Vitamin B deficiency which is reported by Rudy and Cohen to occur in some cases of loosening of the teeth.
They observed increased vascularity of the periodontal membrane in the acute cases which led to loosening of the teeth without obvious mechanical causes and also that the oral lesions tended to clear up with the administration of Vitamin B complex, or some of its components such as nicotinic acid or riboflavin, irrespective of the control of the diabetes.

Coated tongue and fissured tongue are reported by Sheppard\textsuperscript{114} to have fairly high incidence (29\% and 35\% respectively) in his series of 100 diabetics, but it seems doubtful whether this is more than a coincidental finding along with other etiological factors.
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104.


CHAPTER IX

GLUCOSE TOLERANCE TESTS AND ORAL SYMPTOMS

One of the problems confronting investigators of diabetes and oral disease is the establishment of base norms from which to evaluate variables, and this would include such considerations as

1. What constitutes diabetes and what is the significance of variations from this pattern?
2. What indices or measurements can be used to determine the observed oral pathology?

The Alabama investigators (Sheridan, Cheraskin et al.)\textsuperscript{5,6,6a} recognised many of the deficiencies of the published work. In the reports of large series of epidemiological determinations in various population samples, the percentage of diabetic cases varied with the method of estimating the blood or urine glucose levels either separately or in combination, as did also the percentage of unrecognised cases.

For example, in screening for diabetic cases using urine samples alone, the percentage detected is about 2 per 1000, using blood sugar screening procedures the percentage rises to 5 per 100. Also, as would be expected,
the higher the age group, the larger the percentage of unrecognised cases.

The value of the statistical tables prepared by these investigators and their conclusions, lies in the fact that they established a base line point of reference of glucose tolerance testing in a sample of 100 patients presenting for routine dental care at a hospital clinic. A complete series of records was made covering extra-oral and intra-oral symptoms, intra-oral signs, and oral radiographic findings, coupled with a one dose three hour oral glucose tolerance test with simultaneous urinalyses at fasting, 30 min, 60 min, 2 hour and 3 hour periods. Every observed sign and symptom in previous reports was recorded and the findings analysed.

Despite the debate as to the criteria for determining what is and what is not true diabetes mellitus, the following grouping was followed:-

Group I Decrease in tolerance with
a. Blood glucose of 150 mg. % or over during 3 hour test PLUS
b. Failure to reach 100 mg. % or below after 2 hours.

TRUE DIABETES MELLITUS
Group II  Decrease in tolerance with
a. Blood glucose of 150 mg. % or over during 3 hour test OR
b. Failure to reach 100 mg. % or below after 2 hours.

INCIPIENT OR PRE-DIABETES MELLITUS

Group III  a. Fasting blood glucose below 100 mg. % AND
b. Level does not rise above 150 mg. % at any time AND
c. Blood glucose level returns below 100 mg. % in 2 hours.

NORMAL CARBOHYDRATE METABOLISM

Group IV  Increase in tolerance with blood glucose never reaching 100 mg. % in any sample.

"FLAT" GLUCOSE TOLERANCE PATTERN

The significant findings of the study were:

1. 2% of the sample were known diabetics before attending for routine dental examination.

2. 26% of the total sample came within the criteria of Group I and a further 17% of Group II (i.e. decreased carbohydrate tolerance).
3. Majority of patients showing extreme increase or decrease in glucose tolerance were females.

4. Every patient with primary presenting complaint of loose teeth (3%) showed decreased glucose tolerance.

5. Negative family history of diabetes proved of little significance in eliminating the possibility of decreased tolerance and possible diabetes mellitus.

6. Extra-oral symptoms (e.g. boils, appetite, fluid intake and excretion, weight) did not provide significant diagnostic information regarding possible diabetes mellitus.

7. Intra-oral symptoms (particularly dry and burning mouth, gingival tenderness and pain to percussion) occurred more frequently in patients with decreased glucose tolerance.

8. Intra-oral signs (e.g. lip dryness, loss of gingival stippling, so called spontaneous bleeding, marked changes in gingival colour, pocket formation, P.M.A. index, tongue colour, tooth mobility, presence of calculus) occurred with greater frequency in patients with decreased glucose tolerance.

9. Radiographic evidence of alveolar bone loss and marginal widening of periodontal membrane, occurred more often in patients with confirmed and possible diabetes mellitus. (Groups I and II).
10. Overall oral findings in extreme cases of increased or decreased tolerance were very similar.

The above summary hardly does justice to the value of the data presented, as every finding is discussed in detail and an attempt made to quantify findings which previously had only been the recording of a subjective assessment either by the patient or the examining clinician.

As a follow-up to the above investigations, the Alabama group 115,115a pursued two main lines both of which yielded important data regarding diabetic and non-diabetic patients. These were:

a. Observations of the Normal Glucose Tolerance pattern and a survey of the oral signs and symptoms, oral radiographic findings, and extra-oral symptoms, and:

b. Blood sugar levels during dental experiences, commencing with levels in the waiting room, effects of sedation on sugar levels, effects of adrenaline in local anaesthetics on sugar levels, and effects of oral surgical procedures on sugar levels.
Of the methods of determining blood sugar previously referred to in this paper, the one selected was the Standard Glucose Tolerance Test, and the physiologic normal was taken following Mosenthal and Barry\textsuperscript{116}, namely a fasting venous glucose level of 100 mg. per cent or less, no venous glucose level greater than 150 mg. per cent, and a return to the blood glucose level of 100 mg. per cent or less at the end of two hours.

The most frequently recorded oral symptoms of the diabetic are stated to be (Knishkowy, Person, Pollack)\textsuperscript{117}

a. Gingival tenderness
b. Xerostomia (dry mouth)
c. Stomatopyrosis (burning mouth)

but there is wide variation between the percentages of diabetic and non-diabetic patients presenting with these complaints as well as between investigators.

The sample comprised a random selection of 100 routine dental patients and each patient was questioned on each of the above symptoms. A three point scoring scale was used, and a glucose tolerance test was carried out as above.

Graphs were constructed plotting the glucose levels of
patients with and without the above symptoms, both singly and in combination, and a further analysis was made on the basis of age as against symptoms and glucose tolerance.

It is interesting to observe that by the Mosenthal and Barry standards all the patients would be normal in the fasting and peak levels of the graphs, but at the two hour determination, all patients would be systemically abnormal.

Of the individual symptoms, burning mouth was more related to a diabetic state as shown by the glucose level than either dry mouth or gingival tenderness. Burning mouth, dry mouth and gingival tenderness as a combination of symptoms, appeared to be more representative of the diabetic state than any one or double combination of these three symptoms. The age factor did not appear to play a role in the relationship of oral symptoms to the glucose tolerance pattern. The above routine classical glucose tolerance test differentiates the symptoms of gingival tenderness, xerostomia, and stomatopyrosis more sharply than the sometimes used cortisone glucose tolerance test. (Ringsdorf, Cheraskin and Keller),¹¹⁸.
In a similar fashion to the above\textsuperscript{119}, the classical extra-oral symptoms of polyphagia, polyuria and polydipsia were statistically analysed. The individual symptoms, when compared to the glucose tolerance pattern, do not differentiate the diabetic from the non-diabetic individual, but the triad of symptoms does appear to be very representative of decreased glucose tolerance, more so than the triad of the oral symptoms of xerostomia, stomatopyrosis and gingival tenderness. Whilst the pattern of oral and extra-oral symptoms is essentially the same, the extra-oral symptoms appear to be a more delicate barometer of the glucose tolerance pattern. Once again, age did not appear to be significant in the relation of extra-oral symptoms to the glucose tolerance pattern.

Reference is made elsewhere in this paper to the twin features of clinical tooth mobility and tooth loss in diabetes noted by various workers, and if not actually stated in the literature, it is implied that there is a linear relationship existing, that is, the higher the blood glucose or the more pronounced the diabetic state, the greater is the tooth mobility and tooth loss. In a series of experiments, Cheraskin and Moller\textsuperscript{120,121,122,123} found that the relationship between these signs and the
Fasting glucose level was more significant than the relationship between the two signs at the routinely accepted two hour glucose level, but that the relationship at three hour level was more clear cut still, (Cheraskin and Flatland)\textsuperscript{124,125}.

An analysis of the mean score values of each sign, either independently or in combination, shows a parabolic graph pattern with the lowest mean mobility and tooth loss values in the 70 to 89 mg. per cent range, depending on the age grouping, in other words the two signs of tooth mobility and tooth loss are associated with both hypo and hyperglycaemia.

These workers felt that the normal range of fasting glucose values was narrower than previously accepted, and lay in the range of 70-79 mg. per cent. Shafer Hine and Levy\textsuperscript{61} quote whole blood values of 60-90 mg. per cent, and serum values of 70-105 mg. per cent as being the normal range, whilst Joslin quotes the U.S.P.H.S. as using a fasting whole blood glucose value of 110 mg. per cent. A further confirmation of this concept that the true fasting glucose level approximates the 70-79 mg. per cent range in perfectly healthy subjects is provided in the reports of Cheraskin and Ringsdorf\textsuperscript{62} and Ringsdorf, Cheraskin and Hollis\textsuperscript{63}.  
In a still later study pursued on similar lines to the above, Keller and Cheraskin\textsuperscript{126,127} found that the relationship between gingival states, (expressed in terms of gingival hue, gingival stippling, gingival bleeding and pocket formation), and fasting blood true glucose, was not as clearly defined as that observed between oral symptoms, dental signs and oral roentgenographic findings and fasting blood true glucose.

Confirmation in parallel, but not identical, terms of the Alabama investigators' findings is provided by Rose, Kuna and Kraft\textsuperscript{128} in a series of biochemical assays of the sera of 24 patients with periodontal disease to determine calcium, phosphorus, sodium, potassium and alkaline phosphate levels.

A finding of lower calcium-phosphorus ratio and increase of alkaline phosphatase was reported, and it was thought that the chemical changes in diabetes and the levels of alkaline phosphatase and 17-hydroxycorticosteroids have carbohydrate metabolism as a common denominator. Their view is that high blood sugar decreases the available phosphorus in the blood leaving only small amounts for regenerating irritated bone structure. They reiterated the now well recognised connection between diabetes,
adrenal function, and carbohydrate metabolism.

A confirmation of the Alabama studies on xerostomia, stomatopyrosis and gingival tenderness is made by Chinn, Brody, Silverman and Di Raimondo\textsuperscript{129} who found in a series of 45 dental patients with these symptoms, 27\% with decreased glucose tolerance and sugar curves which were consistent with the diabetic or pre-diabetic state.

It should be noted here that the data reported since the mid 1960's has been far more comprehensive in its coverage of the observed facts, far more exhaustive in the statistical analyses, far freer of observer bias, and hence far less open to criticism of the conclusions drawn, than previous studies,\textsuperscript{130,40,111,107,131} etc. This does not detract, in the writer's opinion, from the intelligent application of intuitive deduction to observed clinical or laboratory findings which may or may not be later confirmed or rejected on the basis of objective statistical evidence. Findings of the kind published in the numerous papers of the Alabama group, if valid, should be capable of being reproduced by others. Gottsegen\textsuperscript{132} stated:

"If the work of the Alabama group can be reproduced and confirmed it offers another valuable series of clues to the detection of
diabetes and pre-diabetes. Just as increased foetal mortality and the birth of babies weighing more than 10 pounds occur more frequently in pre-diabetic mothers, just as recurrent hypoglycaemia may be an early hint of a subsequently developing diabetes, just as retinopathy, nephropathy, or the absence of deep reflexes may be the initial findings in a patient without overt symptoms of diabetes, so may these dental findings stand in relation to pre-diabetes and diabetes”.

Immediately following in the wake of the published work of the Alabama group, Shannon et al. produced a series of papers which drew entirely different conclusions from glucose tolerance and related studies. The earliest studies (Shannon and Gibson)\textsuperscript{133,134,135,136} were on a male draftee population between the ages of 17-22 years, who were given conventional three hour oral glucose tolerance, cortisone-supplemented glucose tolerance, and post-prandial glucose tolerance tests subsequent to an assessment of their periodontal status. The periodontal index used was that described by O’Leary et al.\textsuperscript{137}. In all these reports, no connection was found between glucose tolerance and periodontal index, and their own summary was that their results could not be compared with the Alabama conclusions as they did not consider their patients' subjective symptoms, their patients were in a restricted age range which included no diabetics, and different laboratory methods were used in determining glucose concentration. Later reports by the same group (Shannon and
Kilgore\textsuperscript{138} and Stein and Shannon\textsuperscript{139}, one of which embraced a study of patients in the 35-55 age group, failed to show any connection between glucose tolerance and periodontal status.

Tuckman, Haslick, Shapiro and Chasens\textsuperscript{140} who summarized the recent conflicting reports up to this date, designed an experimental study which aimed at the minimising of all factors which would interfere with an objective assessment of the true relationship of periodontal disease to glucose tolerance, a situation later commented upon by Campbell\textsuperscript{40} where he notes that

"To compare two groups of patients among whom there is more than one variable does not allow for a true comparison or evaluation of the effect of the diabetic state on the periodontal tissues".

A random selection of 41 dental outpatients was made, aged 25 to 44 years, along with 13 random selected dental students in the same age group. In this age group, periodontal disease could be expected to be present in varying degrees, and the mid-decade selection starting point was consistent with the recommendations of W.H.O. Every subject had a minimum of 20 teeth in occlusion and no cases of anterior open bite were included to minimise the chances of occlusal factors affecting the periodontal
status. Diet preparatory to testing was controlled to ensure that test deviations would not be attributable to carbohydrate deprivation (Standard two and three hour oral glucose tolerance testing involves 12 hours pre-test fasting). No systemic disease was present and there was no previous diagnosis of diabetes in the patient although 44% gave a positive family history of diabetes (father, mother, brother, sister, child, grandparent, uncle, aunt). No patient was on any medication known to affect glucose tolerance.

The test dose consisted of 7 oz carbonated flavoured beverage (Glucola) containing 75 gm. of glucose, a preparation which had been previously shown to reduce nausea and psychological factors in absorption from the gastro-intestinal tract. Venous blood plasma was used in an automated technique (Hoffman) for the glucose determinations, the P.I. score used was the "mesial method" of O'Leary\textsuperscript{137} and, following the University Group Diabetes Program Method\textsuperscript{141}, a single numerical score value was used for the result of the entire glucose test, rather than individual scores for the fasting, one hour, two hour and three hour values.

To avoid subjective factors, the P.I. scores were
determined before the glucose tolerance testing, and an independent laboratory performed the plasma glucose determinations.

An exhaustive statistical analysis is given of this comprehensive experiment and it was shown that the glucose tolerance of patients with the most severe periodontal disease (P.I. mean of 5.61 and mean age of 38.7) was statistically significantly different to the glucose tolerance of patients with the least periodontal disease (primarily students with a P.I. mean of 2.31 and mean age of 28.7).

They conclude:

"Despite the fact that the mean ages of the two groups were significantly different, the group differences in glucose tolerance remained significant even when the "f" value was adjusted for these age differences. Therefore, the group differences in glucose tolerance scores cannot be attributed to the age differences between the two groups of subjects".
REFERENCES: CHAPTER IX


CHAPTER X

PERIODONTAL AND BONY LESIONS IN DIABETES

RADIOGRAPHIC STUDIES

Some observations as to distinct clinical periodontal features associated with diabetes are made by Hirschfeld who also gives detailed case histories and illustrations of six cases which had come under his care. In reviewing previously published work he stated that he was inclined to believe that in some cases the mouth picture might be accounted for by causes other than the diabetes, which seemed to him to be merely coincidental. He did, however, suggest that two clinical entities were intimately associated with diabetes, namely

1. acute gingival abscess (sometimes multiple), and
2. sessile or pedunculated proliferations or polyps that protrude from under an abnormally heavy, usually unbroken marginal gingiva, which they force away from the tooth surface.

He states, further, (and illustrates the point from a clinical history), that either of the above manifestations may be seen in patients who are apparently not diabetic, but that they occur so much more often in association with
diabetes than without it that the presence of one or both of these symptoms warrants an immediate laboratory examination.

Radiographic evidence of periodontal pathology is offered by Butz\textsuperscript{144} and Weichert\textsuperscript{145} and later by Rutledge\textsuperscript{146}. Butz describes "sporadic periodontosis" amongst 67 cases of diabetics and then a "greater degree of osteoporosis in nearly all cases" which is not designated as "periodontosis", whilst Weichert examined 50 diabetics radiographically and described periodontosis as being present in 68% of his cases (34 patients). Also he describes a further 10 cases as showing evidence of "preparadentosis", namely early bone atrophy with enlargement of marrow cavities and widening of the periodontal membrane. None of his juvenile diabetics (i.e. up to age 12), showed any evidence of inflammatory lesions or radiographic evidence of periodontosis.

Sheppard's\textsuperscript{98} report on a radiographic study of 13 patients between the ages of 8 to 19 years indicates he found little or no bone resorption except in one severe case, but he comments that there is a large incidence of unusual alveolar resorption in diabetics between the ages of 15 and 40 years which can hardly be attributed to
local causes and which is not found in healthy persons.

In making an assessment of the above observations it should be borne in mind that 80% of clinically normal dentulous patients show radiographic evidence of periodontal disease. (Fixott\textsuperscript{147}).

The work of Rudy and Cohen\textsuperscript{99} was widely quoted in the decade subsequent to its publication. In keeping with the thinking of its era they state

"the periodontium of patients with untreated or inadequately controlled diabetes presents a characteristic picture; loosening of the teeth and pain, hypertrophied inflamed gingival papillae, bleeding and pain of the gingiva and periodontium, gingival abscess and excessive polyoid proliferation growing from under the free margin of the gum".

Rutledge\textsuperscript{146} made a study of the incidence of diabetes in 20 juvenile patients aged 8 to 19 years. He assumed that if a metabolic disorder, as such, found in adult diabetics, was responsible for the periodontal manifestations, the same lesions should occur in juveniles with the same disorder. He postulated that an adult with diabetes of long standing would have lowered resistance to periodontal breakdown due to the influences of acidosis, dehydration and diminished vascularity of alveolar bone, and conversely the resistance of a young
person would be much greater. He evaluated

1. The full medical histories.

2. The clinical observations of inflammatory conditions and other abnormalities of their mouth and jaws.

3. The complete radiographic studies of the teeth and jaws.

All patients were receiving the same therapy of insulin and dietary control and were all sugar free and stabilised. (An incidental finding in many (90%) of his cases of juvenile diabetics is relatively large crowns and small roots in the radiographs).

As a result of the studies he was not able to confirm the earlier conclusions of Zilz\textsuperscript{79}, Hilming\textsuperscript{144} and Sheppard\textsuperscript{98} and he concluded that marginal horizontal and vertical alveolar atrophy, widening of the marginal periodontal membrane space, and gingivitis, could be found alone or together, irrespective of diabetes.

The fact that diabetes appears to follow Mendelian laws of transmissibility by a recessive gene leads Rutledge to suggest that "a history of every patient suffering from periodontosis should include an inquiry into the endocrine background of the family".
Two groups of researchers who later published work which modified their earlier conclusions were Sheppard\textsuperscript{114} and Rudy and Cohen\textsuperscript{112}. Their previous work was reported in 1936\textsuperscript{98} and 1938\textsuperscript{99} respectively.

Rudy and Cohen made a full radiographic and clinical survey of 22 diabetic patients and in 12 of these made histopathologic studies by biopsy also. They raise the question of the difficulty of determining cause and effect with the presenting symptoms and whether the oral manifestations are due to the diabetes or whether other factors are operating. It is important, they say, to connect the time of onset of oral symptoms in relation to the development, severity and complications of the diabetes. They distinguish between oral lesions in the acute "uncontrolled" and chronic "controlled" stages of the disease, and state that soft tissue disturbances occur mostly in the former but can occur in the latter.

Periodontosis was observed in only 3 of the 22 cases but presented typical symptoms. Two of the 3 cases of periodontosis were adults in middle life and all three were, with the exception of the diabetes, reported to be free of other endocrine disorders, at least clinically. Diabetic neuritis (all 22 cases at some period) and diabetic
neurogenic bladder (1 case) occurred, both of which conditions are thought to be linked with Vitamin B deficiency. It would be, however, highly speculative, to link vitamin deficiency with the periodontal conditions as their role is still uncertain, and even the present (1973) state of our knowledge does not tend to incriminate disturbed carbohydrate metabolism in the etiology of periodontosis per se.

As part of their studies on glucose tolerance patterns, the Alabama investigators 148,149,150,151,152,153 endeavoured to connect those with radiographic findings, and it will be recalled that the two notable features are alveolar bone loss and marginal periodontal widening. Using a long cone technique on the upper and lower anterior teeth, and a scale of values for the marginal periodontal widening and the amount of bone loss, it was found that there was a greater correlation of the alveolar bone loss than the marginal periodontal widening with the glucose tolerance curve suggestive of diabetes, but also that the combination of the two symptoms was more representative of the diabetic state than individual correlation of either finding. The evidence also suggested that the age factor played a role in the relationship between alveolar bone loss and glucose metabolism.
The often stated connection of calculus with alveolar bone loss was investigated as a corollary study, and it was found that the combination of the presence of calculus with co-existing alveolar bone loss and periodontal widening was the combination which best distinguished diabetic from non-diabetic patients on the basis of glucose tolerance patterns.

A sample of 100 cases of diabetes was reported on extensively by Sheppard, including 12 cases of juvenile diabetes (under age 21), although in the balance of the patients their ages were between 21 and 70 years. No actual blood sugar figures are quoted, but, by description, 52% had mild diabetes, 30% moderately severe diabetes, and 18% severe diabetes. (Of the severe cases 75% were 20 years or less). The long list of symptoms, with their incidence is as follows:

Stomatitis: History of in 2%
Burning Mouth: Subjective symptoms 2%
Ulcers: History of or actually present 4%
Enlarged Tongue: 3%
Geographic Tongue: 3%
Smooth Tongue: 1%
Coated Tongue: 29%
Red Tongue: 3%
Fissured Tongue: 35%
Burning Tongue: 2% (occasional symptom)
Painful Tongue: 1%
Xerostomia: 6% constantly; 20% occasionally;
8% rarely.
Acetone Breath: nil
Foul Odour: 10%
Circular Caries: 2% atypical cervical erosion
Unusual Calculus Deposits: 20%
Unusual Amalgam Failure: nil
Burning Under Dentures: nil
Periodontal Breakdown: no specifically typical lesions.

Sheppard's data and methods are open to a legitimate degree of criticism, particularly the size and source of his sample, all of whom were chronically sick hospitalized patients and who would therefore, in all probability, show an increased incidence of, for example, coated tongue and foul odour, compared with a larger or different series of patients. He concedes that nearly all symptoms of periodontitis that can be seen in a normal population can be seen in diabetics, and that if oral hygiene is good, we expect to find, and do find, normal gingivae. The early bone loss, however, appears to be linked with the diabetic state, and the initial lesion appears to be alveolar resorption with gingival inflammation and other conditions merely following. When the bone has mostly resorbed, the gums are thick, hypertrophied, and reddened, with deep pockets, polyp formation and periodontal
abscesses. These conditions, of course, can all be observed in non-diabetics.

A more meaningful series of studies than the above was made by Lovestedt and Austin\textsuperscript{154}. They investigated 503 diabetics and 1023 matched controls, and graded the severity of the periodontal disease as follows:

- **Grade 0:** Gingivae normal or patient edentulous.
- **Grade 1:** Slight gingivitis with slight bony involvement.
- **Grade 2:** Bony involvement, but no more than three teeth to be extracted.
- **Grade 3:** Bony involvement of more than three teeth requiring extraction, but less than all teeth requiring extraction.
- **Grade 4:** Bony involvement requiring extraction of all remaining teeth.

In the diabetic group there was a higher incidence of periodontal breakdown in Grades 2, 3, and 4, than in the controls, and also the percentage of edentulous patients was greater, indicating that tooth loss as a whole was higher for the diabetic group. The authors point out that they are reticent to say diabetes causes periodontal clasia and quote von Muller\textsuperscript{157} who also states that
periodontoclasia often occurs with systemic diseases without being the cause of them.\textsuperscript{27,59,156,72}

In a combined clinical and histopathological study, Ziskin et al.\textsuperscript{155,96} reported on 94 juvenile diabetics, aged 4 to 19 years, whose duration of the disease was 3 months to 14 years, and analysed 81 of these by statistical methods. (13 cases were omitted where there was a complicating racial factor).

Ziskin's x-ray examination of 40 of his cases showed no appreciable loss or decalcification of alveolar bone, and root development was within normal limits. One radiograph is published, however, of a female age 22 years, with 7 years duration of diabetes which shows extreme periodontosis-like features with deep pocketing and resorption of the maxillary sinus floor in the upper second premolar and first molar region.

There is an obvious emphasis in the literature of the immediate post-war period on the relationship of systemic conditions to the oral manifestations of these diseases, particularly in so far as they affect the periodontal tissues.\textsuperscript{27,158,159,59,59a}
Becks\textsuperscript{160} had previously recognised that it was impossible to establish one uniform cause for periodontosis, and that exogenous and endogenous factors played a part in its etiology, but he quotes the fact (Breuer) that increase in the blood sugar level, and deviations from normal values for blood cholesterol, potassium, calcium, bilirubin, uric acid etc., (disturbances of general metabolism), may be associated with marginal inflammatory conditions (gingivitis) but periodontosis does not develop unless abnormal anatomic and functional conditions are also co-existent.

Boyle\textsuperscript{161} also recognised the dualistic etiology of periodontal breakdown and described it as the end result of a combination of adverse local and systemic factors. The immediate cause of the disease in all instances was recognised as local, but the local tissue reactions which tended to prevent invasion by bacteria or to protect against mechanical injury were always dependent for their effectiveness upon systemic factors. The influence of vitamins and hormones were cited as examples of experimental evidence where the systemic factor played a part in the development of periodontal disease.

Even greater stress was placed on systemic factors by
Cohen\textsuperscript{162}, Stahl\textsuperscript{156}, Burnett\textsuperscript{163} and Sandler and Stahl\textsuperscript{164}. Cohen agreed that diabetics were notoriously prone to infections, but that infected periodontal lesions were secondary to osteoporosis of the alveolar bone. He describes the mechanism of the cause of osteoporosis as follows

"In diabetics the liver is incapable of maintaining the blood sugar level. The sugar absorbed from the intestinal tract is no longer stored in the liver as glycogen, and the blood sugar rises to high levels. At the same time, the production of sugar from protein and fat in the liver continues unchecked. Under normal conditions when there is a rise in the blood sugar, this conversion is inhibited. Thus, in the diabetic, the prolonged use and waste of protein for energy results in a loss of the substance needed for bone matrix and other protein tissues. Osteoporosis follows, and osteoporotic bone is a fertile field for secondary infection".

Stahl\textsuperscript{156} reported the early results of systemic disease states affecting the alveolar tissues in a random selection of 300 hospitalized patients, and in a later report (Sandler and Stahl\textsuperscript{164}) increased the sample to 1299 patients, their findings, therefore, being worthy of note on the basis of the size of the sample alone. In the first sample, the list of diseases present (number of cases listed) were:
**GROUP A.**  
Addison's Disease  1  
Anaemia  3  
Arteriosclerotic  4  
Arthritis  13  
Asthma  7  
Bronchiectasis  16  
Carcinoma  28  
Cardiac Decompensation  20  
Cholecystitis  1  
Cirrhosis  6  
Diabetes  16  
Duodenal Ulcer  47  
Glomerulonephritis  6  
Hepatitis  2  
Hydronephrosis  4  
Hyperthyroid  1  
Leukaemia  3  
Syphilis  7  
Multiple Sclerosis  9  
Pancreatitis  1  
Parkinson's Disease  1  
Pyelitis  1  
Raynaud's Disease  1  
Tuberculosis  8  
Ulcerative Colitis  1  

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The control group of non-systemic diseases was listed as:

**GROUP B.**  
Appendicitis  4  
Anal Fistula  3  
Benign Tumor  2  
Cellulitis  6  
Dermatitis  3
Drug Reaction 5
Eye Infection 11
Fracture and Dislocation 30
Haemorrhoids 12
Hernia 16
Varicose Veins 18
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The ages of the patients ranged from 22 to 69 years, the systemic diseases in all instances had been present 1 year or more, and radiographic studies were made on all patients.

The specific findings reported in this study were:

a. Alveolar crest resorption was more severe with increasing age.

b. The severity of alveolar crest resorption is not correlated with the duration of the systemic disease, but patients in Group A show statistically more severe resorption than Group B.

c. The increased alveolar resorption associated with aging appeared aggravated by the presence of systemic diseases of Group A.

d. The lamina dura was intact in more instances in Group B than Group A.

e. Rapid and slow alveolar resorption occurred equally in both groups.
f. The degree of resorption in anterior and posterior regions was on a par.

g. The most severely affected regions of resorption were the maxillary molar and mandibular incisor regions.

h. The standard error of difference for the resorption was calculated for the two groups and the differences were found to be statistically significant.

Stahl places as much importance on the "aging factor" as he does on any specific disease entity in the course of periodontal breakdown. He concedes, with other investigators, that abnormal metabolic and biochemical process deplete tissue resistance and produce periodontal lesions by different mechanisms, and that the prolonged periods of nitrogen imbalance associated with wasting diseases deplete tissue reserves and impair the antibody mechanism. Gingival tissue and periodontal bone are subject to continuously repeated local irritation and trauma, and it is probable that the superimposition of local trauma or dysfunction on tissues with depleted resistance will produce periodontal lesions more readily and they will respond to treatment more slowly.
According to these investigators, the most significant diseases in this regard are endocrine dysfunctions (including diabetes), malignant neoplasms, and cardiovascular diseases (including nephritis).

Further support for this metabolic concept is provided by Kerr\textsuperscript{165}, who, quoting Coller\textsuperscript{166}, indicates that in an individual unable to carry out normal reparative procedures because of protein deficiency, periodontal disease will progress more rapidly than in the individual who can repair tissue normally. Periodontal disease may render it difficult, if not impossible, to control the blood sugar level in the diabetic and the individual may go out of control because of the destructive process in the periodontium with associated infection.

The only other recorded comparison of a series of diabetic patients is one by Mohnicke and Ulrich\textsuperscript{167} who investigated the oral conditions of 222 diabetics with no apparent (note!) vascular pathology in other parts of the body. Of this number, 39\% had periodontal breakdown of some degree. Of another series of 278 diabetics with systemic vascular changes, 69.9\% showed symptoms of periodontal disease. They recognised, as do others, that many other factors influence bone loss, but they make an interesting comment that there
is a link between oral and dental diseases and short and stocky types with diabetes.

Their patients, presumably, were of German stock, and whilst it is an established fact that older, more obese patients tend to be more prone to develop diabetes, it is interesting to speculate what are the racial or anthropomorphological factors concerned in its etiology. Would it be possible, for example, to speculate that the series of Viennese diabetics recorded by Zilz (1915) were predominantly of Jewish origin?

Resch in summarizing previous work, confirms the occurrence of such features as lowered oral tissue resistance, osteoporosis of the alveolar bone, and degenerative changes in the blood vessel walls of young diabetic patients, (vide also, Provenza et al. Williams) but indicates from two case histories that factors apart from primary endocrine disturbances play a part in the breakdown of dental structures, and thus links with the stress syndrome described by Selye.

A summary of these two histories will elucidate the point:
Case 1: Patient, woman, aged 49, uncontrolled "brittle" (i.e. unstable (Joslin)) diabetes, periodontal treatment (including gingival curettage) 4 years; teeth hypersensitive; good oral hygiene; heightened fear of losing teeth; active caries; smoking - 20 cigarettes per day; x-rays show advanced generalized alveolar resorption in both arches involving bifurcations and trifurcations.

Comment:
Are the complicating factors (a) smoking, (b) psychoneurosis?

Case 2: Patient, woman; history of unhappy childhood (what relevance!) Age 29 diabetes mellitus first diagnosed; age 30 - slight caries, no periodontal pathology; age 33 - electroencephalographic diagnosis of idiopathic convulsive disorder; age 36 - complained of toothache and bleeding gums; localized periodontal disease diagnosed; age 38 - suffering from exulsive exhaustion and not following diabetic diet; age 39 - suffering from urticaria, and late pregnancy suspected but not confirmed; age 40 - advanced periodontal disease, active caries and
poor oral hygiene; extractions carried out without complications, and full upper and partial lower denture inserted; age 41 - cardiac changes suspected, later treated for typical active Graves disease with diabetic uncontrol; still later treated for "neurotic dermatitis"; age 43 - treatment for further urticarial eruption.

Comment:
(a) no insulin treatment recorded, (b) other endocrine factors operating (Graves disease), (c) psychoneurotic factors have an important if unspecific, bearing on the course of disease.

The lack of evidence relating general health states to periodontal disease, does not mean, according to Loe\textsuperscript{171} that systemic conditions do not play a significant role in periodontal disease. The only systemic conditions which this investigator believes play a part in the development and progression of periodontal disease are pregnancy and diabetes mellitus, and he considers full medical histories important in periodontal prognosis and treatment.

In endeavouring to correlate periodontal disease with diabetes, Glavind, Lund and Loe\textsuperscript{130} studied a series of
102 patients (all males) between 20 and 40 years of age, 51 of whom were controlled diabetics and 51 non-diabetics. The same type of gingival inflammatory lesions were seen in both groups in the whole age range, and the gingival condition, as distinct from more advanced tissue breakdown, was not influenced by the duration of the diabetes or the insulin requirement. Deeper changes (i.e. loss of fiber attachment, pocket depth, and loss of alveolar bone) were the same in both groups up to the age of 30 years, but in the 30 to 40 age group there was a slight increase in the diabetic group of all these features, and there was a greater incidence if the diabetes had been present for 10 years or longer, and if there were retinal angiopathic changes as well. The conclusion drawn was that the changes seen in long standing cases were attributable to an unknown deficiency in the resistance of the diabetic periodontium.

Hove and Stallard\textsuperscript{110} who made clinical, x-ray and biopsy studies of diabetic and non-diabetic groups, were not able to substantiate any difference made by the diabetic state on periodontal breakdown, but rather that it was related to increasing age and the accumulation of calculus and plaque alone. They did, however, observe a higher incidence of vascular changes in the diabetic periodontium.
On the other hand, Cohen and his co-workers, who also used recognised scoring methods for gingival condition, presence of deposits, and periodontal deterioration, and in addition followed his group of 21 diabetic women and 18 non-diabetic women over a period of three annual examinations, found that the diabetic group had significantly more gingival involvement, loss of attachment, and tooth mobility, than the non-diabetics. The soft deposit scores, in the diabetics, were significantly lower.

Campbell also nullifies the suggestion that controlled diabetics do not demonstrate a larger incidence of periodontal disease than non-diabetics and showed that 47.1% of his diabetics had a periodontal index (Russell's method) of 9.8 or more, whereas only 30.4% of non-diabetics had a score at or above this level.

Apart from occlusive vascular disorders which are treated in detail elsewhere in this paper, (Oral Histopathology), there appears to be one other factor reported as being involved in periodontal breakdown in diabetics, namely, β-glucuronidase. Non-diabetic patients with periodontal breakdown show higher β-glucuronidase levels in the saliva than those without. In diabetic patients,
the $\beta$-glucuronidase is raised before periodontal destruction sets in, and it falls again as the disease progresses. Further work is needed to substantiate the significance of these findings or otherwise.

The work of Williams and Mahan\textsuperscript{173} on the treatment of periodontal conditions in diabetics is reported in another section of this paper (Dental Patient Management).
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CHAPTER XI

ORAL HISTOPATHOLOGY IN DIABETES

Some of the earliest histologic studies on diabetic oral tissues were done by Gescheff\textsuperscript{82}. At this period of time it was known that blood levels of cholesterol and fats were raised in diabetes, and in 80% of his sections he observed that round cell infiltration occurred in the subepithelial connective tissue with fatty depositions as well. He drew the conclusion that the fatty infiltration of the inflamed periodontal tissues were the result of the diabetic lipoaemia which lowers the resistance and decreases the healing capacity of periodontal lesions, and he suggests that these findings explain the predisposition or constitutional tendency to periodontosis. In this respect his reasoning is analogous to the conclusions of Glickman\textsuperscript{174} regarding a "bone factor" in periodontal breakdown.

Ziskin et al.\textsuperscript{80,96} reported on a group of juvenile diabetics. The histopathological studies showed a thickened margin and increased crevicular depth, hyperplasia of epithelium and connective tissue, increased glycogen deposition (using Best's carmine stain), increase of fibroblasts and prominence of the capillary bed, and a
reduction of inflammatory exudate in the corium. The gingivae are said to be violaceous in colour, which is attributed to some obscure factor connected with diabetes.

In seeking explanations for the observed changes, these investigators suggest, following the work of Mosenthal and Loughlin\textsuperscript{175} that the frequently observed suboptimal Vitamin A plasma levels in diabetics may be a possible factor in the gingival changes. They noted that in the two cases controlled by diet, without insulin, the degenerative and inflammatory changes were particularly severe, and were attributed to the patients' nutritional and metabolic status. In the insulin treated cases, the insulin itself as well as the diabetics may be an agent causing a metabolic change in the gingival cells and their conclusions were that the changes observed could be of a protective nature.

Other workers who followed up the histopathological work of Ziskin and Glickman included Boyle\textsuperscript{176} Ray\textsuperscript{177} Ray and Orban\textsuperscript{178}, and Provenza et al.\textsuperscript{169}.

Boyle\textsuperscript{176} carried out histologic and radiographic studies on the alveolar structures of dogs. He took as proven
the fact that heredity, endocrine disturbances and vitamin deficiency diseases affect the periodontal tissues, but stated that whilst reports in the literature indicated that alveolar bone reacted to systemic influences as did bone in other parts of the skeleton, (see Glickman\textsuperscript{179,180,180a}) there was evidence that exceptions to this general rule occurred. In his radiographic and histologic studies of dogs in which the alveolar bone was partially replaced by abnormal trabeculae and fibrous tissue, other parts of the skeleton were unaffected. It seems possible, therefore, that alveolar bone may undergo selective absorption in certain systemic diseases for reasons which even now may not be understood.

Human biopsy material was used in the studies of Ray\textsuperscript{177} and Ray and Orban\textsuperscript{178}. In a series of 30 diabetics, in which they describe 13 cases as being poorly controlled, 11 as fair, and 6 as well controlled, they noted an increased percentage of the following lesions as against non-diabetic samples:

a. Accumulation of plasma cells and lymphocytes extending well into the tissues even in the absence of actual epithelial ulceration and inflammation.
b. Lymphocytes often localized in the papillary layer and invading the epithelium.

c. Degeneration of the collagenous fibres observed in both the papillary and reticular layers of the gingiva.

d. Thickening and hyalinization of blood vessel walls, sometimes leading to complete obliteration. Fibrinous thrombosis was observed.

e. Hyaline and calcified bodies present in a large number of specimens.

The conclusions from this study were that the diabetic state seems to modify the reaction of the gingival tissues to breakdown, partly by lowering resistance and partly by inducing vascular damage, and that it might be directly responsible for the degeneration of collagenous fibres due to increased protein breakdown. The validity of both of these deductions has been amplified by later workers, notably, Keene\textsuperscript{181}, Campbell\textsuperscript{131,105} and Mackenzie and Millard\textsuperscript{106}.

In the later work\textsuperscript{178} a series of 36 diabetics and 40 non-diabetic individuals were investigated and it was observed that none of the diabetics were entirely free from gingivitis, but there was a correlation between the severity of the gingivitis and the control of the diabetes.
In addition to being confirmatory of the earlier observations additional histopathological features such as epithelial surface character change from stippled to smooth, lack of keratinization and epithelial intranuclear vaculolization were reported.

Ray and Orban thought that some of the changes in diabetics may represent an increased tissue reaction or resistance to local irritation and in this respect their conclusions are analogous to Ziskin who described the gingival changes in diabetes as of a protective nature.

There is an obvious and increasing awareness in the work published in the last decade or so, of the significance of degenerative vascular changes in the production of bone loss in both diabetic and non-diabetic subjects.

In a properly controlled and well documented series of 60 diabetics, 64 suspected diabetics, and 54 arteriosclerotic and non-diabetic people, Mackenzie and Millard could not demonstrate that arteriosclerosis in diabetes had an effect on alveolar bone loss, and concluded that diabetes mellitus in itself could not be associated with increased alveolar bone resorption. They recognised, however, the limitations of their study, particularly:
1. Higher average age (57 years) than most similar studies.

2. Diabetic patients had no previous knowledge of their condition and hence the duration of the condition and its influence on alveolar bone loss was unknown.

3. Biopsies of gingivae were not performed - the arteriosclerotic changes were diagnosed by retinal changes alone.

Whilst it is well recognised that retinal changes are an accurate barometer of generalized arteriosclerosis, the work of Stahl, Witkin and Scopp\textsuperscript{182} shows conclusively by histopathological methods that the great majority of diabetics have an associated degenerative pattern in the gingival blood vessels. They showed that the blood supply of the gingival vascular bed is affected by thickened arterioles, splitting of the elastic membrane and fuchsinophilia of the entire thickened vessel wall (P.A.S. stain). Cahn makes an editorial comment on the significance of this work, and cites instances where changes in the blood vessels of tissues excised during oral surgical procedures have given a clue to impaired cardio-vascular function. Belting, Hiniker and Dummett\textsuperscript{183} also hold the opinion that occlusive vascular disorders
render periodontal disease more severe in the diabetic patient, and Stahl\textsuperscript{184} reiterated that research in the vascular area should lead to more precise understanding of response to carbohydrate metabolism.

The concomitant diabetic vascular pathology is further elucidated by Russell\textsuperscript{185}. In his series of patients (37 diabetics with an average age of 17.75 years and 35 matched controls with an average age of 20 years) an endeavour was made to eliminate factors apart from the diabetes which could alter the vascular pathology. Accordingly, the following criteria had to be fulfilled in both the experimental and control groups (where applicable).

1. All patients under 38 years of age to eliminate senile arteriosclerotic changes.
2. No presence of other systemic disease.
3. Diabetes had to be clinically diagnosed before age of 30.
4. Duration of diabetes less than 10 years.
5. Pregnant patients excluded.

The proportion of smokers was kept identical in both groups and no patients with a family history of diabetes mellitus was included. Gingival biopsies were made and stained with haematoxylin and eosin.
In the control subjects the biopsies showed normal blood vessels whereas 14 out of 37 diabetics showed a variety of changes including swollen endothelial cells, obliteration of vascular lumina, thickening of basement membrane between epithelium and connective tissue, and hyalinization of the vessel walls.

The vascular changes appeared as early as two weeks after a positive diagnosis of diabetes mellitus and appeared to justify being called direct "diabetogenic" changes.

Campbell\textsuperscript{105} reported on the differences between the general arteriosclerotic changes in the peripheral system, and those occurring in the retinal vessels and renal glomeruli. The latter have two components:

a. PAS positive staining substance and
b. internal swelling

and in the case of the retina, proliferation of the vessels also. Later sections examined under the electron microscope, show thickening and folding of the capillary basement membrane in diabetic glomerulosclerosis accompanied by the precipitation of "hyaline" material derived from the cytoplasm of the endothelium and a proliferation of those same cells. Other structures which show the same changes are the placentas of diabetic mothers,
amputated extremities, gastric mucosa and gingivae.

Campbell puts down the greater likelihood of periodontal disease to the fact that the oxygen consumption rate in the gingival tissues has been shown to be significantly reduced in diabetic patients, but Glavind, Lund and Loe are by no means so definite, and refer to these changes reflecting some "unknown deficiency in the resistance of the diabetic periodontium".

In a further study Campbell (1971) using light microscope methods to examine diabetic gingivae found P.A.S. positive fibrils is in the media of the blood vessels, proliferation of endothelial cells, disorientation of cells, poor differentiation of internal and external elastic membranes, and overall increase in thickness of vessel walls. Electron microscope studies showed thickening of basement membranes of diabetic, compared with non-diabetic subjects to the extent of a difference of 363.3A at the 1% level. The thickness varied not only with the age of the patient, but also between patients of the same age. (ref. Anapolle and Albright and Newcomb).

In the early part of this paper, diabetes was classified as follows:
1. Overt diabetes.
2. Chemical diabetes.
4. Prediabetes

The last mentioned being a state existing genetically from conception till the first abnormal glucose tolerance test in a patient who has a family history of diabetes. The work of McMullen et al.\textsuperscript{188} endeavoured to ascertain by histopathological methods, inter alia, what changes, if any, took place in the gingival tissues in such a diabetically predisposed individual before the disease could be diagnosed by other methods.

The sample comprised five overt diabetics, five chemical diabetics, ten prediabetics and seven normal controls, and the prediabetics were further classified genetically by family history.

Class A Both parents diabetic. 5 patients.
Class B One parent diabetic. 1 patient.
Class C More distant relationship diabetic. 4 patients.

Sections were prepared of buccal tissue which included interdental papilla, attached gingiva and alveolar mucosa, and three staining techniques (P.A.S., Verhoeff's elastic tissue stain and Fulmer's oxytalin stain) were
used to differentiate between normal basement membrane and "hyaline" deposits, elastic tissue and collagenous fibres.

In the specimens of attached gingiva where all showed inflammatory changes the vascular pathology was not evaluated, but in the alveolar mucosa there was capillaropathy in eighteen out of the twenty diabetics as shown in the table below, and normal vascular morphology in all controls.

<table>
<thead>
<tr>
<th>Overt</th>
<th>Chemical</th>
<th>Genetic</th>
<th>Genetic</th>
<th>Genetic</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dia-</td>
<td>Dia-</td>
<td>Predia-</td>
<td>Predia-</td>
<td>Predia-</td>
<td>Controls</td>
</tr>
<tr>
<td>betics</td>
<td>betics</td>
<td>betics</td>
<td>betics</td>
<td>betics</td>
<td>_______</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>_______</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thickened Small Vessel Walls</th>
<th>4</th>
<th>5</th>
<th>5</th>
<th>1</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Vascular Morphology</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

When studied with the light microscope, there appeared to be disruption of both the alignment and shape of the endothelial cells lining most of the small vessels, and in some instances the endothelial nuclei appeared to have been almost "squeezed out" into the lumen of the vessel.
The periendothelial area or basement membrane appeared thickened and positive P.A.S. staining, probably due to deposits of glycoprotein. No direct relationship could be found between the clinical and histological pathology.

These investigators point out the danger of drawing too generalized conclusions from their observations and suggest that investigations at a biochemical level, which would certainly precede observable histopathological changes, would throw more light on the etiology of the changes in periodontal disease complicated by diabetes mellitus.

However, it is reasonable to conclude that any gingival vascular lesion may well upset the delicate mechanism of blood flow across vascular beds, and thereby alter the local resistance and tissue repair mechanisms of such individuals. As has been suggested elsewhere in this paper, prolonged sub-optimal oxidation and nutrition of the tissues as well as sluggish removal of waste metabolites may well explain, at least in part, the decreased resistance to infection of the diabetic periodontium\textsuperscript{188a}.

Basically, these same conclusions are supported by the work
of Barrett, Cheraskin and Ringsdorf\textsuperscript{189}, and Frantzis Reeve and Brown\textsuperscript{190}. These last mentioned researchers took their studies through electron-microscope quantitative measurements of diabetic and normal gingival blood vessels and found that the mean width of basement membranes in diabetics with periodontal disease was approximately four times greater than in normal patients or non-diabetics with periodontal disease. In diabetics the basement membrane of the blood vessels is thickened by increase of its substance, and production of collagen fibres could be observed within its structure, both features contributing to impede oxygen transfer and waste elimination.

By a consideration of the implications of the vascular pathology, it is not difficult to extend the concept to the effects on pulpal tissue. Cohen, Shklar and Yerganian\textsuperscript{191} who examined the pulpal tissue of Chinese hamsters with hereditary diabetes mellitus, found definite degeneration of pulpal fibroblasts and odontoblasts. When the pulp is involved by carious activity, its resistance appears to be reduced compared with control animals, so that severe inflammatory reaction with abscess formation and necrosis may occur. Epstein\textsuperscript{192} states that the vascular changes present in advanced diabetes are frequently
reflected in the pulp and may cause generalized tooth
pain not attributable to any other cause, whilst
Rosenthal\textsuperscript{193} goes so far as to say that the arteritis
of diabetes may cause pulpitis and/or loss of vitality
in clinically sound teeth.

Differentiation of blood vessel structure on a histo-
chemical basis is reported on by Keene\textsuperscript{181}. In a series
of 12 diabetic patients and 17 non-diabetic controls,
serial sections of clinically normal palatal mucosa were
evaluated. Using several staining techniques, he found
an aldehyde-fuchsin and acid-orcein positive deposition
of dye, primarily in the adventitia of the diabetic
arterioles compared with non-diabetic vessels. The
change was demonstrated in 91.6% of the diabetics but
only 29.4% of the controls. The stained material is
believed to be elastic tissue.
REFERENCES: CHAPTER XI

82. Gescheff, G. Some Lipoid Investigations of the Periodontium in Diabetes, Parodontium 3:117,No.4 1931.


CHAPTER XII

EXPERIMENTAL ANIMAL STUDIES IN DIABETES

Following the discovery (Dunn\textsuperscript{194}) that the drug alloxan had a specific necrosing action on the islets of Langerhans, a large amount of experimental work was undertaken and reported by Glickman\textsuperscript{174,179,195,180}. Up to this point experimental diabetes had been produced in animals only by pancreatectomy and injections of pituitary extract, but it was now possible to obtain increase of blood sugar levels without disturbing the tissues.

Alloxan (mesoxalylurea), is the ureide of mesoxalic acid and its similarity in structural formula to uric acid, the irritant agent in gout, is well known.

Both uric acid and alloxan selectively destroy the \(\beta\)-cells of the islets of Langerhans. Injections of alloxan bring about firstly a brief hyperglycaemia, a transitory hypoglycaemia, followed by a sustained chronic diabetic hyperglycaemia. After cessation of the alloxan injections, reparative changes take place in the islet cells as time progresses.
A series of experiments were conducted on rats to determine the effects of alteration of systemic background to bone areas subjacent to areas of gingival inflammation. Both radiographic and histopathologic studies were made, and the groups were divided so that half the experimental animals were fed on normal diet and half on a starvation (water only) diet.

At the time of sacrifice of the animals, both the jaws, vertebrae, long bones and other bones, along with organs such as the pancreas, were investigated microscopically.

In the first published account of this work, Glickman reported as follows:

"1. Bone of the jaws undergoes changes similar to other bones as the result of generalised disturbances of systemic origin.

2. In the absence of gingival inflammation, bone loss may occur as a result of generalized skeletal disturbances.

3. Inflammation in the gingival crevice may result in bone resorption and reduction in the height of the interdental septa in the absence of generalized skeletal disturbance.

4. The severity of bone loss subjacent to gingival inflammation is increased by generalised disturbances of systemic origin.

It is suggested that since a 'bone factor' of systemic origin regulates the progress and severity of bone loss in periodontal breakdown both in the presence and absence of gingival inflammation, research in the field should be directed towards determining the nature of this 'bone factor'."
In later reports Glickman was more definite in the interpolation of his findings on rats as they related to human diabetics and stated, in summary, that

1. Diabetes per se is not responsible for specific gingival changes or the onset of gingival disease (he noted no gross pathological differences between the gingival mucosa, interdental gingival papilla and gingival crevices of control and diabetic animals).

2. A tendency towards periodontoclasia which is systemic in origin may result in a loss of both supporting bone in the absence of gingival changes in a large percentage of diabetic animals. There is no correlation between the severity of the changes and the degree of hyperglycaemia and pancreas disturbance.

3. The degree of bone resorption in individual diabetics in whom the alveolar bone is affected by generalized osteoporotic changes may expectedly be more rapid than it would be in the absence of diabetes.
4. There are no microscopic features of periodontoclasia in diabetics which designate it a clinical entity (vide. Mallowalla and Koppikar).  

5. The fact that a large percentage of diabetics show no alveolar bone changes, discourages the assumption that wherever periodontoclasia occurs in afflicted individuals, its origin and progress are primarily motivated by the diabetes.  

6. Where pathological changes occur in the alveolar bone of diabetic animals, comparable alterations are also observed in other bones of the skeletal system.  

7. Control of diabetes will not of itself be a remedial measure in the alleviation of the periodontoclasia.  

8. Evaluation of periodontoclasia in diabetics should take into consideration –  
   a. The periodontoclasia may have been present at the onset of the diabetes.  
   b. The periodontoclasis may be potentiated by alterations in local environment.
c. The periodontoclasia may be primarily associated with systemic disturbances unrelated to the diabetes.

Whilst reservation must necessarily apply to the transference of conclusions on animal material in the interpretation of human symptoms, the general validity and trend of Glickman's work must be accepted. The field of further purposeful study was thereby narrowed down and subsequent investigators mainly confirmed the above findings or amplified the detail of the investigations.

Later work with experimental animals and laboratory studies throw up some interesting sidelights, which bear principally on the vascular abnormalities, but also on the disease process itself.

Rosen and Enquist observed that granulating wounds in experimental animals healed more quickly than sutured wounds. In the latter, sutures elicited intense inflammatory reactions, and in some instances, total wound breakdown. Whilst there have been instances in human subjects of sutured wounds breaking down after oral surgery, it is by no means general (vide infra Dental Patient Management), but it is quite feasible that tension
on systemically abnormal tissues would predispose to slough formation. In contrast the blood vessels in the bed of a granulating area would normally proliferate and extend without interference or pressure, even if at a slower rate due to partial vascular obstruction.

Bissada, Schaffer and Lazarow\textsuperscript{198} studied the pathological changes in the supporting tissues of alloxan - diabetic rats and confirmed previous studies that no specific changes could be observed in the gingiva or periodontal ligament without local irritant factors, but that the severity and progression of the disease was much greater in the diabetic animals than in the controls. In their reports on blood vessel changes, they noted the same features in the diabetic and non-diabetic animals under light microscope examination, and indeed they could not confirm similar changes to those reported in human material by Campbell\textsuperscript{131} and Russell\textsuperscript{185}. They suggested that electron microscope study of human gingival material would probably give a more comprehensive picture of the nature and distribution of diabetic capillaropathy, and this is reported elsewhere in this paper\textsuperscript{190}.

Amongst workers with experimental animals who subscribe to the views of local and systemic factors operating to
cause tissue breakdown in diabetes are Shklar, Cohen and Yerganian\textsuperscript{199} who studied changes in diabetic Chinese hamsters whose diabetic status is more akin to human diabetes than the condition induced by alloxan. In their view, diabetes acts on the periodontal tissues in an "anti-anabolic" manner. This means, literally, "against the process of building up (tissue)", and they contend that the severe bone loss in the experimental animal is presumably the result of local irritation and pocket formation acting on bone and connective tissue altered by the diabetic state. As the experimental animals had their blood sugar levels controlled by insulin, the theories of tissue breakdown discussed elsewhere in this paper are relevant.

Glickman\textsuperscript{200} found that not only soft tissues, but hard tissues, in alloxan-diabetes-induced animals, showed slow healing of periodontal wounds due to decreased fibroblast production and proliferation. Delay of healing and increased inflammatory response in extraction wounds of alloxan-diabetic animals was observed by Chiba\textsuperscript{201}, also Murata et al.\textsuperscript{202} who stated that the acute inflammatory phase remained longer after surgery and it took longer for the fibrin network of the blood-clot to be absorbed in the post-extraction period.
An experimental contribution of considerable merit was made by Abbey et al. who studied the effect of Streptozotocin-induced diabetes on the healing of artificially produced tongue wounds in rats. (Streptozotocin, which is chemically related to alloxan, is a broad-spectrum antibiotic and antitumour drug which acts as a specific irreversible poison to the cells of the islets of Langerhans with otherwise low general toxicity. Pancreatic insulin stores are almost completely exhausted within 24 hours of the injection of streptozotocin).

The rats used in the experiments had blood glucose levels of 250 mg. per cent, as above, and ++ + + glucosuria. Lesions were produced on the lateral edges of the tongue, measuring 1.0 mm x 1.0 mm x 1.5 mm, with rongeurs, and the animals were sacrificed at the eight different post-operative periods as below. It was noted that in the control animals, the islets of Langerhans were normal in size and number, but in the experimental animals they were reduced in both size and number. Observations on the lesions were:

<table>
<thead>
<tr>
<th>6 hours</th>
<th>Diabetic Animals</th>
<th>Non-Diabetic Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inflammation more intense</td>
<td>Cleaner wound surface</td>
</tr>
<tr>
<td></td>
<td>More surface bacteria</td>
<td>More oedema</td>
</tr>
<tr>
<td></td>
<td>More necrosis</td>
<td>More polymorphs</td>
</tr>
<tr>
<td>Time</td>
<td>Diabetic Animals</td>
<td>Non-Diabetic Animals</td>
</tr>
<tr>
<td>-------</td>
<td>----------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
</tbody>
</table>
| 18 hours | More acute inflammatory changes  
More bacterial colonies               | No significant bacterial growth      |
| 24 hours | No evidence of migrating epithelium                                                | Migrating projections of epithelium  |
| 48 hours | Early evidence of epithelialization                                               | Chronic lymphocyte-predominated inflammation  
Migration of fibroblasts            |
| 4-5 days | Fully epithelialized  
Lymphocyte and histiocyte infiltration  
Fibroblast infiltration | Fully epithelialized  
Lymphocyte and histiocyte infiltration  
Fibroblast infiltration |
| 6-7 days  | Foreign body response and reaction severe  
Reversal of chronic to acute (Polymorph) inflammation | Normal foreign body response         |
| 14 days  | Acute inflammatory signs  
Breakdown of epithelium  
Bacterial growth | Healing complete                       |
| 21 days  | Normal                                                                 | Normal                                |

The above comparison shows that the experimental wounds in diabetic animals are firstly slow to start the healing
process, then become epithelialized but subsequently show a partial breakdown before finally healing the same as the controls, there being a time lag in this instance of approximately seven days behind the controls.

It would be clear also that the above process involves the mechanism of the disruption of vascularity (Malins). Early stages of healing tissue must have large oxygen supply and remove extensive waste material, both organic and metabolic, for cells that are actively synthesising protein. Diabetics show reduced capillary and vessel activity to angiotension, and delayed clearance of intradermal saline, resulting in a reduced perfusion of oxygen and nutrients.

A vital point which scarcely rates a mention in the enormous volume of literature on the relationship of diabetes and oral disease is the question of what part the treatment of the diabetes either by insulin or oral anti-diabetic agents, plays in the production of oral lesions.

As early as 1936, Houssay indicated that pancreatectomy in the dog produced degeneration of parathyroid cells with a fall in blood calcium levels, and also a decrease
in plasma sodium, chloride, alkaline reserve and total CO₂, a picture which is strongly suggestive of diabetic acidosis.

Puche et al.²⁰⁵ found that the administration of crystalline insulin to thyroparathyroidectomised rats raised their calcium and phosphorus plasma levels, clearly indicating that the insulin itself promotes bone resorption. The increase of insulin produced by the administration of glucose in normal animals did not however, alter the calcium plasma level. In vitro experiments where chick embryo frontal bones were cultivated with crystalline insulin showed an increased rate of resorption. An instance is also cited in Puche's paper of a schizophrenic patient being treated with insulin convulsive therapy (150 units crystalline insulin) whose plasma calcium rose from 10.5 mg. per cent to 11.7 mg. per cent one hour and 14.4 mg. per cent three hours after injection.

Whilst it is possible to suggest that in human subjects the increased blood calcium could well be mobilised from active areas of bone such as the marrow, it is equally possible that alveolar bone which is undergoing constant anabolic and catabolic changes could be selectively resorbed in this process, thus helping to produce the
clinical and radiographic picture that is observed in cases of diabetes mellitus. Any conclusions in this regard would have to be made in a series of radiographs taken of uncontrolled diabetics before treatment and subsequently under insulin therapy. Other extraneous considerations would doubtless complicate the picture.
REFERENCES: CHAPTER XII


CHAPTER XIII

ORAL BACTERIOLOGY AND INFECTION IN DIABETES

It is clear from observations recorded elsewhere in this paper that many investigators consider the oral infections of diabetics can be more virulent than in normal persons. Uncontrolled or acidotic diabetics are prone to systemic mycotic infections, and all diabetics, in whatever state of control show an increased susceptibility to invasion by gram-negative organisms, particularly those involving the urinary tract\textsuperscript{206}.

Oral infection of any kind in the diabetic intensifies the diabetes. Chronic periodontal disease or chronic periodontal infection, when eliminated, may stabilise the patient on lower dose of insulin than formerly, whereas an acute alveolar abscess is a serious complication which may precipitate diabetic acidosis with alarming rapidity. Burket\textsuperscript{163} and Burket and Sindoni\textsuperscript{35} comment on the lack of resistance to infection in diabetics, and this, as mentioned earlier, is due, at least in part, to the impaired blood supply and transfer of nutrients.

Other indirect effects are depressed activity of Vitamin C
and increased requirement of Vitamin B complex (McCarthy and Shklar)\textsuperscript{207}. They found there was a close similarity with the periodontal, oral, mucosal and lingual signs and symptoms in uncontrolled diabetes and those occurring in Vitamin B complex deficiency.

The dermatologic symptoms of diabetes can also be adequately explained on the basis of a conditioned nutritional deficiency (Rudy and Hoffman)\textsuperscript{208}, but it should also be remembered that \textit{candida albicans} is also usually associated with genital skin lesions in diabetics\textsuperscript{34}. Candida albicans has also been isolated more frequently from the saliva of diabetics than from the saliva of normal individuals (Weinstein et al.)\textsuperscript{210}, and as some clinicians\textsuperscript{209,35} report an "impression" that "dry socket" occurs more frequently in the diabetic than normal, even when the disease is controlled, it is possible that both this organism as well as other gram-negative and gram-positive organisms play a part in its etiology.

As to the bacterial colonization of the mouths of diabetics, Massler\textsuperscript{211} and Stahl\textsuperscript{212} make specific mention of distinctive bacteriological features. Massler examined a series of 289 diabetically controlled and diabetically uncontrolled patients and found higher than average incidence of
staphylococcus aureus and of haemolytic streptococcus
the pillars of the fauces and lower anterior gingivae,
whilst Stahl showed an abnormal growth of haemolytic
organisms occurred in 25 out of 38 diabetic patients
surveyed, although he found no correlation between the
increase in severity of the diabetes and the amount of
haemolytic growth present.

Yet another factor affecting tissue resistance and break-
down is the presence of immune bodies in the blood,
which are in the gamma globulins. In diabetes, as in
starvation states, the gamma globulins may disappear
from the blood, thereby rendering the tissues less resis-
tant to breakdown and infection (Pollack et al.)\textsuperscript{213}.
The diabetic patient is initially on a handicap because
of his negative nitrogen balance which was particularly
significant in the pre-protamine zinc insulin era, where
there is a drainage of body proteins in addition to
inadequate calcium metabolism for rebuilding depleted
reserves.
REFERENCES: CHAPTER XIII


CHAPTER XIV

DENTAL PATIENT MANAGEMENT IN DIABETES

The dental treatment of the diabetic patient rightly comes at the conclusion of this study, as it can only be properly carried out in the light of a full knowledge of the disease processes previously outlined. Despite the handicaps which attend the diabetic patient undergoing dental treatment, there are few contraindications to properly planned surgical intervention. In an uncontrolled diabetic, only the mildest and most atraumatic of scaling procedures should be undertaken and any more extensive treatment is definitely barred until the diabetes is stabilised, this being, of course, apart from emergencies.

Also, without medico-dental liaison, there will be unnecessary distress to the patient, and it is worthy of note that a leading medical journal devoted two editorials to this subject within a three year period.214,215 To omit a full history-taking before treating a diabetic is a cardinal clinical sin, and it would also be unwise to take the patient's word only for his treatment regime without medical verification.
Assessment of the patient's needs and treatment planning are also at least as important as, if not more important than, the actual carrying out of the procedures. For instance, it may be unwise to be too radical in rendering the patient edentulous despite a poor periodontal prognosis, as mucosal soreness under a denture may be intolerable, and cause the patient painful sensations often referred beyond the denture bearing area. On the contrary, chronic infection cannot be left untreated, whether it be in the form of periodontitis or apical areas, as in both instances, the insulin requirement may be increased or else wildly fluctuating, and in addition, an acute infection may supervene resulting in a medical emergency.

In addition to a consistent diabetic control pattern, the fluid and electrolyte balance is important both pre-operatively and post-operatively, and vitamin supplementation, has, probably on an empirical basis, been recommended to assist tissue healing.

For dental procedures on ambulatory patients the avoidance of pre-operative stress is desirable for all, let alone diabetics. Some comfort for harrassed surgeons, however, may be taken from the reports of
Cheraskin et al.\textsuperscript{219,151} who found that the blood sugar levels in the dental waiting room were not elevated above normal for the patient, whether diabetic or non-diabetic, whilst awaiting treatment. They found that the levels of sugar in both groups was more likely to be modified by their reaction to previous dental experiences rather than the diabetic state, and furthermore, premedication in the form of 1\textfrac{1}{2} gr. secobarbital 45 minutes pre-operatively had no effect on the blood sugar levels. This view is not shared by Silverman\textsuperscript{220} who states that hyperinsulinaemia may be initiated by a stressful dental procedure.

A note of caution should also be sounded regarding the administration of steroids over a period of time to patients who may be suffering from oral mucosal lesions and/or who may be potentially a pre-diabetic. Mason\textsuperscript{221} records a case where benign mucous membrane pemphigoid had been treated with local triamcinolone 0.1% and subsequently oral prednisolone 1 mg. b.d. increasing to 5 mg. t.d.s. over two months, resulting in symptoms of loss of weight, lassitude, weakness of arms and legs, polyuria, polydipsia, wasting of proximal muscles in upper and lower limbs and a positive G.T.T., all of which add up to a positive diagnosis of diabetes. The
process is normally reversible on cessation of steroid therapy.

The four areas in which decisions must be taken in treating a diabetic patient are

(a) Choice of anaesthetic.
(b) Control of infection.
(c) Extent of treatment.
(d) Pre and post-operative care.

(a) Choice of Anaesthetic:
For simple procedures surgical or otherwise, local anaesthesia is first choice in the dental situation. Some authorities\textsuperscript{222,35} condemn the use of solutions containing any adrenaline or its derivatives at all, because of its ischaemia-producing properties and also its potential danger in raising the blood sugar through the breakdown of liver glycogen. Others consider it to be of little consequence in the normally used dosages.\textsuperscript{41,223} Sutherland\textsuperscript{224} wisely suggests reducing the adrenaline to a minimum consistent with obtaining proper pain control, and remarks that nor-adrenaline, present in some formulations of local anaesthetics, whilst it does not tend to produce hyperglycaemia, should not be used because of the increased local ischaemia it produces.\textsuperscript{193}
Preparation of mucous membrane surfaces with iodine-containing solutions is contraindicated because of possible necrotizing action.35

General anaesthesia is not necessarily contraindicated in diabetics nor are intravenous sedation, procedures using valium, methohexital or Jorgensen's technique.225 Proper premedication and general anaesthesia may be more desirable than local anaesthesia in allaying fear105 which may cause adrenalin levels to rise far higher than those attained by a local anaesthetic injection and resulting in the release of hepatic glycogen thence to raised glucose level in the blood.

Whilst nearly all inhalational anaesthetic agents cause some degree of hyperglycaemia, fluothane and nitrous oxide/oxygen are the least harmful. Under normal circumstances, a diabetic undergoing dental surgery may be safely induced with pentothal and relaxants, intubated, and carried through on maintenance with nitrous oxide/oxygen and a minimum supplement of fluothane.226,227

(b) Control of Infection:
The principles governing the administration of antibiotic agents in diabetics are the same as in other
situations, namely it should not be routine procedure unless a fairly severe bacteremia is likely to be produced by the surgical intervention. Tahl and Colwell recommend starting therapy three days prior to operation and continuing for three days post-operatively or until patient is afebrile. Williams and Mahan suggest a routine commencing one day pre-operatively and continuing for ten days post-operatively. Their antibiotic combination of choice is 300,000 units procaine penicillin G and 0.5 gm. streptomycin b.d. intra-muscularly.

A well cared for mouth in a patient requiring few extractions or moderate gingivectomy should not require antibiotic cover but a dirty mouth in a debilitated patient requires adequate protection.

All periapical and periodontal foci of infection must be eliminated but a properly treated pulpless tooth should be regarded conservatively.

(c) **Extent of Treatment:**

This is governed by the effect of the overall trauma to the patient, and, particularly if general anaesthesia is decided upon, the more work that can be done in one
session the better. In some instances it may be preferable to use general anaesthesia for an extensive procedure rather than several shorter sessions under local. It is contended\textsuperscript{217} that general surgery is not done in stages on a diabetic, so why oral surgery? Surgery must be as atraumatic as possible and suturing procedures should be such that tension, and hence tissue necrosis, does not occur. On the other hand, protection of blood clots is necessary to obviate the possibilities of osteitis.

Under antibiotic cover as mentioned above, it is possible to do periodontal surgery and exodontia in one planned procedure. In a series of 9 patients who were treated and followed up for three to seven months (Williams and Mahan)\textsuperscript{173} seven showed a reduction of insulin requirement after elimination of oral infection, the daily average reduction being 30 units of N.P.H. insulin.

(d) Pre and Post-Operative Care:
Most diabetic patients presenting for dental surgery, if not on one of the oral hypoglycaemic agents, will probably be taking one of the long-acting insulins P.Z.I. (Protamine Zinc Insulin) or N.P.H. (Neutral
Protamine Hagedorn). P.Z.I. has an initial intensity of action of 0 to 12 hours and a total duration of 24-48 hours. N.P.H., which is more commonly used, is a neutral, crystalline protamine zinc insulin which acts more promptly than P.Z.I. in reducing the blood sugar, and has an initial intensity of action of 8-10 hours and a total duration of 24-30 hours.

N.P.H. is given once daily and supplemented, if necessary, according to metabolic needs, with regular or crystalline insulin (quick acting).

Various routines for pre-operative management are given\textsuperscript{217,228,229,230} but a satisfactory regime is as follows:

Surgery should be early in the day if possible, and if general anaesthesia and/or extensive procedures are contemplated, hospitalization should be for two days before operation for a routine work up including daily fasting blood sugar tests, blood urea/nitrogen determinations to check on kidney function, W.B.C. (to rule out any undetected infection), haemoglobin, (should not be lower than 10.5 gm%), and antibiotics if deemed advisable.
For surgery done under dental office conditions using local anaesthesia, no change in the patient's insulin routine is usually necessary, and the normal dose of long acting N.P.H. may be taken in the morning.

With extensive procedures, and general anaesthesia, where the patient has to fast for 4 to 6 hours pre-operatively, half the dose is given four hours pre-operatively and the second half immediately post-operatively. In addition a slow intravenous infusion of dextrose should be started 4 to 6 hours before operation and allowed to run for six to eight hours. The average requirement is 750 ml to 1000 ml of a 5% solution, and it should be administered until all nausea has subsided and oral feeding can be resumed without undue distress to the patient.

Post-operatively the blood sugar and urine should be checked at regular intervals and any adjustments made to the insulin requirements with crystalline (quick-acting) insulin.

A close check should be made on the patient post-operatively for insulin reactions, as the insulin requirement may diminish in the 12-24 hour period after
surgery due to removal of infection. Also it is essential that proper fluid and dietary balance be established as quickly as possible to facilitate healing.
REFERENCES:  CHAPTER XIV


