

PERIODONTAL DISEASE

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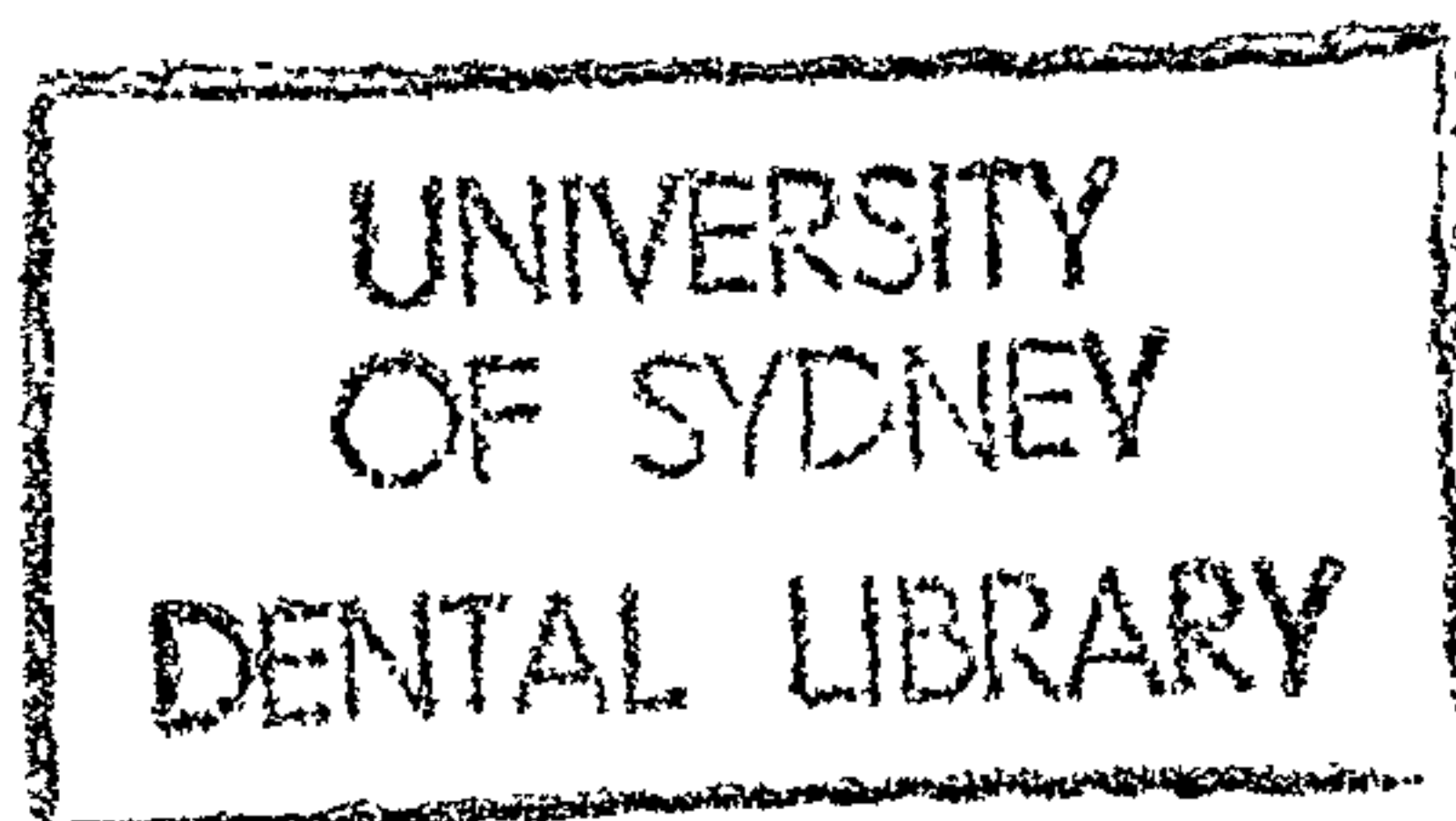
DIABETIC ADULTS

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1. PREFACE

In an attempt to investigate the possible changes in periodontal tissue which may take place in diabetic patients, a detailed study of the available literature concerning periodontal disease in individuals suffering from diabetes mellitus was made, and a clinical survey of patients with diabetes mellitus was undertaken; a matched control group of an equal number of non-diabetic patients who otherwise were apparently in good health were also examined.

Diabetes and diabetes mellitus are used synonymously in this thesis. A study of the medical literature, and discussions with the physicians at the Royal North Shore Hospital and the Royal Prince Alfred Hospital failed to give diagnostic facts which would permit a definite positive or negative diagnosis in every case. The glucose tolerance test whose figures were considered diagnostic for diabetes vary from one clinic to the other, and only additional signs and symptoms could help determine whether a patient should be considered diabetic.

This investigation used diagnosed diabetics attending the Royal North Shore and the Royal Prince Alfred diabetic clinics. The potential diabetic was eliminated from the control group by recording any family

history of diabetes. The survey in this thesis is not new in concept, however potential diabetics have been eliminated from the control group, and more variables have been controlled than in most other studies and the oral hygiene index has been added.

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2. INTRODUCTION

Diabetes Mellitus is a disease complex which shows a state of impaired carbohydrate tolerance due to an absolute or relative lack of insulin action. Dietary carbohydrate having entered the blood as glucose is inadequately taken up and utilised by some tissues. Symptoms result from glycosuria caused by the raised blood glucose level. Diabetes is associated with two types of complications which are the most serious aspects of the disease. The main specific complications are ketosis and a microangiopathy. The main non-specific complications are atheroma and infections. The reason for the complications are unknown, but the duration of diabetes is a major factor. (53)

Physicians have for a long time considered that oral symptoms and signs may be the first to suggest the presence of diabetes mellitus. Comroe, Collin and Crane (40) in 1954 listed the following oral signs and symptoms as manifestations of diabetes mellitus. Many dental reports list the same signs and symptoms in various combinations:-

1. "Dryness of the mouth and thirst" (3) (32) (91) (116) (143) (144).
2. "A deep red colour of the mucous membrane" (63) (99) (132) (143).

3. "Swollen highly inflamed, dark red gums, frequently detached from the tooth, chronic gingivitis almost always present" (1) (3) (32) (86) (91) (99) (116) (125) (143) (157) (169) (170).
4. "Pus readily expressed from periodontal pockets and gum papillae, 'pyorrhoea' almost universal among diabetics" (186) (116) (144).
5. "Teeth frequently become loose, this may seem to occur almost overnight" (86) (99) (116) (132).
6. "Increased sensitiveness about the neck of teeth (86) (116) (143).
7. "Ready bleeding from the gums on slight trauma" (1) (3) (91) (99) (116) (132).
8. "Frequent formation of salivary calculus" (3) (86) (143) (144) (157).
9. "At times an enlarged, thick, fissured, raw-ham coloured tongue" (63) (86) (99) (132) (143) (157).
10. "Frequent occurrence of dry sockets".
11. "Presence of acetone on the breath when the diabetes is not under control" (143) (144).

The older experiences with diabetes as described in the literature may not bear a close relationship to present day experience, for the history of diabetes falls

into several eras. The pre-insulin era before 1921, the Banting era from 1921 to 1938 and the protominc zinc insulin era since 1938. The results in the therapy of this disease complex have changed with each of these eras. Prior to the introduction of insulin the juvenile diabetic survived on the average of only one year. These patients did not have a chance to develop the oral changes which require longer periods of time.

In the Banting era diabetic patients were just kept alive. It was in these last two eras that so many oral lesions of diabetes were described. With the introduction of protominc zinc insulin, there was a definite improvement in the results of therapy. The case with which a patient could be kept in a positive nitrogen balance improved the physiological status of the patient. Under this therapy, the type of oral lesions changed and their occurrence decreased. It will however, take many years before the full impact of this improved therapy can be finally evaluated (116).

Before discussing the relationship of periodontal changes with diabetes mellitus, a general knowledge of the history of the etiology and a general knowledge of the pathological changes in diabetes mellitus will help to interpret more intelligently any periodontal disease

associated with this disease. The dental literature was reviewed from 1940, as the improved insulin treatment may be assumed to have had its effect by this time.

Many authors (11) (60) (63) (81) (93) consider that diabetes mellitus does not cause periodontal disease, but rather that it increases the severity of periodontal disease if it is present. Considering this fact the survey recorded in detail the main local causes of periodontal disease, such as debris and calculus rather than merely recording the frequency of tooth brushing, for a patient may use a tooth brush many times a day and still have a high debris and calculus score. Tooth brush frequency was recorded in the survey so that a comparison of results may be made with other studies which only used tooth brush frequency. The time that a patient was known to be diabetic was recorded, for time is important in the development of vascular changes which many authors (25) (120) (148) (154) report occur also in the periodontal tissues.

Each diabetic patient examined was paired with a healthy patient who was the same age, sex, race, in the same socio-educational strata and who was considered to be non-diabetic if she/he had a negative family history of diabetes mellitus.

The survey was of 53 diabetic outpatients attending the Royal North Shore diabetic clinic and of 54 diabetic outpatients attending the Royal Prince Alfred diabetic clinic, the age requirements were 25-49 years. The control patients were suitable hospital employees of the Royal North Shore Hospital, and patients attending non-medical clinics at the same hospital.

The aim of the survey was to study the relationship between diabetes mellitus, the duration of the disease and the severity of periodontal tissue changes.

3. SURVEY OF LITERATURE

A. THE HISTORY OF THE AETIOLOGY OF DIABETES

Diabetes was described clinically and also named before the Christian era by Aretaeus (138) who lived from 30-90 A.D. Galen (56) who lived a century later was the first person to attempt an explanation of the symptoms; he suggested that the weakness was in the kidneys and that they could not hold back the "water". Galen (56) further suggested that urine consisted of unchanged drink.

The sweetness associated with diabetic urine was first noted by Susruta (20) in the fifth century, and in the ninth century by Avicenna (43). Seven hundred years later Willis (165) re-emphasised this fact. Sydenham (48) who lived in the seventeenth century considered that the nutritive elements of the blood were not properly prepared for assimilation and so "they pour through the kidneys and the flesh, and strength melts away". Morton (106) in 1698 was the first to note the hereditary character of the disease. In 1776 Dobson (46) proved that there was "sweetness" of the blood serum and assumed that there was excessive accumulation of sugar in the blood stream, which he considered was formed by some abnormal body fermentation.

Cawley in 1778 (30) was the first to associate diabetes with pancreatic disease, it was about the same time that Cullen (42) applied the adjective "mellitus" to the name of the disease. Increased chemical knowledge which developed in the later part of the eighteenth and the early part of the nineteenth century enabled Bernard (15) in 1887 to discover glycogen, he also described the glycogenic function of the liver. Bernard (15) further suggested that the liver supplied sugar to the circulation from its glycogen store in the intervals between food intake.

In 1846, Bouchardat (22) attempted to produce diabetes in a dog by removing the pancreas, but was unsuccessful. Mering and Minkowski (100) in 1890 accidentally observed diabetes in dogs who had undergone a pancreatectomy. This discovery, which dominated medical opinion for the next thirty years concerning the aetiology of diabetes, emphasised an earlier observation of Langerhans (83) that there were certain groups of island cells in the pancreas whose function appeared to be unrelated to that of the pancreatic parenchyma. Ople (111) in 1901 discovered degenerative changes in the pancreatic islet cells in human patients suffering from diabetes. These biological discoveries led to the development of the hypothesis which in 1909 Woodyatt

(166) expressed in the following words:-

"Diabetes mellitus is a disease in which the body has in part lost its ability to utilize sugars. Sugar arrives at the point where it should burn, but fails to do so, and accumulating in the blood creates a hyperglycaemia. Disregarding accessory facts which may play a part, we can say that ultimately the failure of sugar combustion in diabetes mellitus depends upon the lack of something derived from the pancreas".

This latter view was generally accepted and Allen's (2) experiments in the next ten years and his dietary control of diabetes led him to the following conclusion:-

"The state of the islands of Langerhans as an internal secretory organ, and as the seat of the specific diabetic disturbance is now as firmly established as any fact in physiology or pathology".

His experiments led Allen (2) to the conviction that diabetes was caused solely by dysfunction of the pancreas and he referred to diabetes as "a unified entity, rather than a disjointed symptom complex". This conclusion did not stand up to the clinical evidence of the next thirty years.

The apparent failure of the islet cells to function led many workers to attempt to isolate an extract of these

cells which would influence the course of the disease. It was Banting and Best (7) in 1922 who were the first to discover a satisfactory extract. This hormone called insulin had a remarkable effect on diabetic patients, and the universally amazing improvement shown by patients, who were treated with it, gave great support to the theory that the pancreas was the seat of origin of diabetes mellitus. It appeared certain that diabetes mellitus was caused by a quantitative lack of insulin, and that a cure was assured as soon as the cause of the pancreatic dysfunction could be discovered.

The discovery of insulin itself, besides being of calculable clinical value, stimulated a great deal of clinical and experimental studies which turned opinion away from Allen's theory of the primary pancreatic origin of diabetes and even from the idea that it is a single disease. In many instances studies of autopsy material, from patients who had died from diabetes, failed to show any characteristic changes in the islet cells (161).

Acute pancreatitis seldom caused or was followed by diabetes (160) (47). Normal insulin values were occasionally found in the pancreas of diabetic patients (139). When the pancreas was removed because of a carcinoma, it was found that diabetes is produced and

controlled by daily doses of forty units of insulin (125). A common clinical experience was that patients require much larger doses than this to control diabetes. In these cases, at least, it seemed that there was something other than a primary quantitative failure of insulin which caused diabetes (159).

A great deal of thought and experimental work was carried out to discover if the various ductless glands play any part in the etiology of diabetes. In 1923 Houshey (74) was able to show that the diabetes that developed after hypophysectomy and pancreatectomy in a dog was materially different and less severe than that which followed pancreatectomy only.

In the nineteenth century, great interest was shown in the function of the pituitary gland, and it was proved that the control of many body functions was maintained by "oscillatory equilibrium" between contra-acting hormones. In some instances this balance appeared to be controlled by the pituitary gland. In 1937 Young (168) showed that daily injections of fresh crude anterior pituitary lobe extracts if continued for two or three weeks produced permanent diabetes in the dog. A most interesting factor was that this effect was not found in puppies or in some other adult species. If large doses

of insulin were administered at the same time, the effects of the pituitary extract were prevented (69). Lukens, Dohan and Voelcott (92) in 1943 confirmed these findings in cats, and showed high fat, low caloric diets nullified the effects of pituitary extracts.

Diabetes was induced in partially depancreatized animals by the injection of adrenal cortical steroids (76) and it was shown that cortical extracts aggravated diabetes in adrenalectomized depancreatized animals. A transient diabetic state was induced in human volunteers by repeated daily injections of adrenocorticotrophic hormone (38). Thyroid secretion would also seem to have some influence, for Houshey (75) in 1944 induced diabetes in partially depancreatized animals by the administration of thyroid extract. If insulin is administered simultaneously to these animals, the development of diabetes is prevented.

Jacobs (78) in 1937 showed that Alloxan, a purine derivative which apparently is not normally found in the human body produced a rapid and selective death of the islet cells of Langerhans. Dunn, Sheehan and McLetchie (49) in 1943 confirmed Jacobs research with Alloxan, which proved of considerable value in experimental work. Whether Alloxan plays any part in the etiology of human

diabetes is still unknown.

The discovery of insulin naturally posed the question of its mode of action, but how and where it acts is still unknown (23). Many of the reactions seem to be reversible and to be controlled by contrary-acting regulators both enzymatic and hormonal. It was thought that insulin influenced the disposal of sugar by the peripheral tissues and by the liver, that it regulated the level of the blood sugar and controlled the formation and breakdown of glycogen. Also it was believed to exert some influence on the fixation of amino-acids and on the regulation of hepatic ketogenesis. These functions may appear diverse, but it is possible that they reflect the consequence of a single catalytic influence on various basic enzyme systems. Support for this theory came from the work of Cori (41) in 1951 who demonstrated that insulin abolishes the effect of pituitary and adrenal cortical extracts in depressing the rate of the fundamental hexokinase reaction in the primary stage of the breakdown of glucose-6-phosphate.

Soskin, Essex, Herrick and Mann (149) in 1938 emphasised the importance of the blood sugar level and theorised on its regulation by hormonal control. They suggested that the blood sugar value at any given moment

reflects the balance between formation of sugar by the liver and its disposal by the peripheral tissues.

Another perplexing problem is the hereditary influence in the aetiology of diabetes. A careful study of the family history has become a very important diagnostic factor. White, Joslin and Pincus (162) in 1934 stated that twenty-five per cent of the population of the United States of America may be carriers of diabetes, and that this tendency is inherited as a mendelian recessive characteristic. Wilder (163) in 1941 suggested that sundry apparently unrelated factors such as trauma, shock, infection and pregnancy may precipitate the onset of diabetes in a susceptible individual.

This incidence of diabetes at different ages and in opposite sexes poses an unanswerable question. Diabetes is much more common after thirty years of age and the incidence in the third decade is almost equal in both sexes, however as age increases diabetes occurs more frequently and with greater incidence in females (48). The clinical course and symptoms of diabetes are more severe in the younger groups.

For a long time, it has been noted that there is an association between obesity and diabetes especially during middle age. Joslin (79) and his co-workers in 1946

emphasised this association and referred to "preglycosuric obesity". Newburgh and Conn (108) in 1939 had shown that in certain cases symptoms disappeared and the glucose tolerance test resumed a normal pattern if a patient reduced his weight. This is the only type of patient in whom a cure has been demonstrated. This observation would appear to contradict any idea of pancreatic exhaustion as a primary factor in the aetiology of diabetes in these cases (84).

A prediabetic stage was suggested from the observations of Barnes and Morgan (8) in 1948, who examined foetal mortality rate in a group of women who developed diabetes at a later date. The figures showed a high foetal mortality rate comparable with the figures which occur in pregnancy of known diabetic women. Barnes and Morgan (8) suggested that this is evidence of an endocrine imbalance which exists before diabetes is clinically diagnosed.

In 1936 Falta (52) after studying the response of diabetes to insulin, suggested that some patients are more sensitive to its action than others. Himsworth (72) in 1935 suggested that diabetic patients can be separated into two groups, insulin-sensitive and insulin-insensitive. In 1949 Himsworth (73) re-emphasised this theory and suggested that diabetes is not a single disease entity but that it should be

regarded as a syndrome which may develop from any one of a number of causes. He contended the one important feature of the syndrome was an elevation of the blood sugar level above normal limits and that the causes of abnormal hyperglycaemia fall broadly into two groups; one group consisted of those cases which result from a primary insulin deficiency or from an inhibition of insulin caused by overfunction of the anterior lobe of the pituitary gland the insulin-sensitive group. The second group included the abnormal hyperglycaemias of obesity the insulin-insensitive group. Himsworth (73) also emphasised that, no matter what the primary cause was, abnormal hyperglycaemia, which was common to both groups, could lead to islet damage and secondary insulin deficiency. This concept offered a possible answer to the clinical improvement which followed careful use of insulin in almost all cases. Dornic (48) in 1951 stated that diabetes mellitus should be regarded as a symptom-complex resulting from any one of a number of causes. He contended that the endocrine balance is the foundation from which comes our understanding of the normal metabolic control of food, but that the primary aetiological factor in human diabetes did not seem to be merely in the disproportion of certain endocrine

secretions.

Hirsky (102) (103) in 1957 endeavouring to give an explanation of these difficulties theorized that the primary cause in diabetes was not in the B-cell production and/or the secretion of insulin, but in an unusually high rate of insulin inactivation by a specific enzyme, insulinase, before insulin reached its receptor. Although this theory was not acceptable in its original form, it opened a new approach to the problem and in a modified form is still a current speculation.

During the fifties and early sixties of the nineteenth century studies brought to light clinical, morphologic and chemical characteristics of the diabetic state before any measurable loss of carbohydrate intolerance. This prediabetic stage is best seen in close relatives of overt diabetics, and the close study of this stage shows that slow, profound and unknown biochemical changes must precede the disorder of intermediary metabolism which we have for years known as diabetes (39) (155).

In 1962, Charles Best (17) listed the following eight possible causes of diabetes:-

1. Defects in the pancreas as a whole including the beta cells.
2. Defects in the formation of insulin.

3. Defects in the liberation of insulin.
4. Abnormal destruction of insulin.
5. Genetic defects involving insulin dependent reactions.
6. Excess of diabetogenic substances.
7. Genetic defects making tissue abnormally susceptible to diabetogenic substances.
8. Genetic defects independent of hormonal actions.

Ditzel and Sagild (45) in 1954 and Camerini-Devalos and his co-workers (27) in 1963 showed that microcirculation changes are characterised by thickening of the basement membrane and proliferation of the endothelium. It is realised that these changes were by far the more dangerous body reactions to this protean disease and that they produce nephropathy, retinopathy, neuropathy, gangrene and coronary disease. The relationship between microangiopathy and the metabolic disorder in food transformation is obscure but is certainly indirect.

McNallin (94) in 1967 classified diabetes into four stages according to clinical signs and symptoms:-

1. Overt diabetes in which all the classical signs and symptoms are seen, including an abnormal tolerance to glucose.
2. Clinical diabetes, in this case abnormal glucose

tolerance is shown after the intake of food or glucose, but without any of the other signs or symptoms of diabetes.

3. Latent chemical diabetes in which abnormal tolerance to glucose is shown upon metabolic stress is produced by the administration of steroids.
4. Prediabetes: Rafael Camerini-Davados (27) defined a prediabetic, as a person who has a normal glucose tolerance test and a family history of diabetes. Thus the prediabetic is usually predisposed and lives as a prediabetic from the time of conception until an abnormal glucose tolerance is evident. This last stage Jackson (77) calls the "genetic prediabetic".

Summary

The search for a unified primary aetiological factor in diabetes is still characterized by uncertainty and the present theories concerning the aetiology may be listed as follows:-

1. Diabetes is the result of a hereditary fault.
The syndrome includes the prediabetic stages, the diabetic stage and the various angiopathy forms.
2. During the prediabetic stage, certain abnormal processes are at work which initiate micro-circulatory changes as well as modifications of insulin output, transport and/or effectiveness.
3. In the vast majority of diabetic cases the level of circulatory insulin seems to be within at least normal range.
4. Recent work indicated the presence in the blood of (a) insulin-inhibiting substances, and
(b) insulin-binding materials.

The metabolism of the insulin molecule may be quantitatively abnormal.

5. There is no present indication as to the organ which is the seat of the primary gene change. Whether it is extra-pancreatic or resides in the beta cells is unknown.

D. PATHIOLOGY OF DIABETES MELLITUS

Present evidence tends to indicate that diabetes mellitus develops as a consequence of a disturbance in the balance between insulin production, on the one hand, and any factors modifying the requirements of it, on the other. The importance which relative or absolute insulin deficiency plays in the pathogenesis of the disease is demonstrated by the success with which most diabetic patients are treated, with insulin or insulin substitutes irrespective of the cause or the type of diabetes.

Most medical opinion, at the present time, is greatly influenced by the evidence suggesting initial regulatory dysfunction of insulin release (167) or of insulin effectiveness (19) rather than to that which indicates a primarily depressed synthesis of insulin.

Modern thought is that insulin deficiency first limits carbohydrate utilisation of normal blood glucose levels, this is compensated for in part at least, by a rise in blood sugar, by means of increased carbohydrate formation and increased glucose liberation from liver glycogen. In most patients, unfortunately, the elevation in blood sugar exceeds renal reabsorptive capacity and the benefit derived from increased utilisation of carbohydrate at the higher blood sugar

level is loss of carbohydrate in the urine. Inadequate glucose utilization despite hyperglycemia stimulates mobilization of fat in the form of fatty acids and their breakdown to ketone bodies in the liver (53a). The latter substances comprise a normal source of energy but in the presence of impaired glucose utilization, may be formed in excess of the capacity of the tissues to utilize them, leading to a rising blood ketone level and ketonuria. Because of the acidic nature of the ketone bodies and the limited renal ability to excrete an acid urine, it is necessary for the kidney to excrete cations with the ketone acids, leading to both sodium and potassium loss (53a).

In unregulated diabetes, the body loses glucose, ketone bodies, cations and water. Dehydration and acidosis resulting from the loss of cations and water, as well as from the excess of circulating anions, further impair the utilization of glucose and increase the insulin requirement, thus aggravating the already serious insulin deficit. Transitory antagonists of insulin action appear in the blood. With increased ketosis and dehydration, coma may supervene. Since insulin is not believed to exert a direct effect upon carbohydrate utilization by nervous tissue, coma is probably due to the direct effect

of acidosis, ketosis, and dehydration on the central nervous system (53a).

That primary lack of available carbohydrate may lead to the syndrome of diabetic coma is well illustrated by the similar syndrome of ketonemia in lactating cows. In these cases excessive milk production results in a negative carbohydrate balance, and ketosis and coma supervene in the presence of hypoglycemia; this syndrome can be dramatically reversed by a single large intravenous administration of glucose (53a).

The pancreas is macroscopically normal except in the rare patient in whom diabetes is due to gross pancreatic damage. The earliest changes in the islet of Langerhans consists of "hydropic degeneration". The most common finding is that first described by Opie (111) in 1901 of hyalinization of the islet cells in patients who died of diabetes mellitus; such changes occur in less than half of the patients with diabetes mellitus, but is rarely observed in patients who are not diabetic.

Bondy (18) in 1967 contends that fibrosis and lymphocytic infiltration of the pancreas are found very rarely and usually in patients who die within a few weeks after the onset of diabetes. He further contends that extensive quantitative studies of the total mass of

the beta cells of the islets of Langerhans in diabetic patients have demonstrated some decrease in all the patients with a severe juvenile form of the disorder and in more than eighty per cent of elderly, obese, nonketotic diabetics (109) (57). Bondy (18) states that the electron microscope promises to reveal changes in nearly every case of diabetes mellitus, and that already more specific perivascular and perigranular lesions are being established.

Extraparacarcatic lesions observed during post-mortem of diabetics are varied and are presumably secondary to the long-continued metabolic disturbances evidenced by hyperglycaemia, lipemia and ketosis, (53a). The distribution and deposition of glycogen are frequently abnormal. Except in the terminal phase of diabetes, glycogen levels in diabetic patients appear to be equal to or higher than those in non-diabetic persons, particularly in the fasting state (53a).

In the kidney an accumulation of glycogen is commonly found in the renal epithelium. Other tissues such as heart muscle, iris and the ciliary bodies of the eye, and the skin are frequently found to contain an accumulation of glycogen. Fatty infiltration and enlargement of the liver are common findings in

untreated diabetos and especially in diabetic children (53a).

Vascular lesions comprising morphologic changes in the intima of venules, capillaries, arterioles and the smaller muscle arteries occur in addition to ordinary atherosomatous and arteriosclerotic lesions in the larger vessels of all diabetics. Whereas the former are confined practically exclusively to the diabetic patient, the latter are found in all patients coming to autopsy, but occur some ten years earlier and with greater severity in diabetics (62) (53a).

Several authors (44) (25) have suggested that not only in diabetics, but even in non-diabetic members of their families, the ground substance of the vascular wall is subtly changed, making it particularly prone to atherosclerosis. In addition, blood coagulation is changed in uncontrolled diabetos as it is in other hyperlipemic states.

The capillary lesion is easily demonstrated in retinal and renal glomerular vessels, with increasing frequency as the duration of the diabetes increases particularly after the thirtieth year (62). The typical lesion of diabetic retinopathy consists of a saccular microaneurysm, most commonly at the level of the venules,

with a halo-like haemorrhage around it, making it visible on ophthalmoscopic examination. Dilation and beading of the larger retinal veins, due to weakening of the basement membrane, are seen earlier. Later stages comprise white exudates, retinal haemorrhages extending into the vitreous with subsequent organisation leading to development of retinitis proliferans, and sooner or later retinal detachment. Diabetic retinopathy is frequently but not always associated with a characteristic lesion of the small vessels of the kidney (53a). The basal membrane of the kidney capillaries and venules, made up of mucopolysaccharide bound to protein, undergoes swelling, reduplication and proliferation towards the lumen. This intramural material becomes impregnated with certain components of the plasma, forming hyalin, which eventually obstructs the lumen in the form of a hyalin nodule. Whereas the characteristic nodular distribution of the hyalin is practically pathognomic of the diabetic state and is known as intercapillary glomerulosclerosis, the diffuse lesion may occasionally be seen in non-diabetic renal diseases (53a).

At autopsy there is frequently found the combination of three distinct renal pathological processes, which have been termed diabetic nephropathy, consisting of

nephrosclerosis, chronic pyelonephritis and intercapillary glomerulosclerosis. The greater frequency of urinary infections in diabetic patients predisposes some of them to the serious complications of necrotising papillitis. With advanced vascular disease, interruption of the blood supply to the papillae leads to the desquamation of their tips and to mechanical blockage of the urine flow (53a).

Specific lesions known as diabetic angiopathy have more recently been recognised in the arterial trunk, consisting of an obliterating endarteritis with marked proliferation of swollen endothelial cells, quite distinct from the fibrosis and hyalinisation seen in arteriosclerosis (53a).

C. TREATMENT OF DIABETES

Since cure of diabetes mellitus is impossible at the present, the objective of treatment is life-long control. The minimal aim of treatment is to prevent ketoacidosis and symptoms resulting from hyperglycemia. In most cases this is easy to attain, but in some unstable diabetics, even this limited objective may be hard to achieve. Prevention of complications, an obvious objective, can only be partially achieved. Finally at least as important as the other two is the obligation to avoid damaging the patient by therapy (18). The methods available for treating the diabetic patient include:-

1. DIET. The role of diet in treating diabetes has been greatly exaggerated. Diabetics have the same nutritional requirements as normal people and these must be supplied. High quality protein, carbohydrates and fats must be supplied; sucrose perhaps should be kept to a minimum because of its rapid absorption. Institution of a low-calorie, reducing diet is important for obese diabetics (18).

2. ORAL HYPOGLYCAEMIC AGENTS. Where diet alone does not control diabetes of the maturity-onset type oral antidiabetic medication may be prescribed. These are sulfonylureas and biguanides. The sulfonylureas (the

main one is Tolbutamide) appear to promote secretion of insulin by the pancreas or they may release insulin previously bound in inactive form.

The diquarides (most common phenformin) are supplied in ordinary or slow release form, its action is not clearly known but it may act by modifying the anaerobic dissimilation of carbohydrate (18).

3. INSULIN. All those patients whose diabetes cannot be controlled with diet or oral drugs must use insulin.

Tolting, Hinkler and Dunnett (11) used the amount and type of medication prescribed to assign a value to the degree of diabetes:

1. "very mild" was assigned to those patients on dietary control only.
2. "mild" to those patients receiving orinase tablets.
3. "moderate" to those patients receiving diabinese tablets.
4. "severe" to those patients receiving 30 units of insulin or less.
5. "very severe" to those patients receiving over 30 units of insulin.

Whatever the treatment, the patient is considered to

be under control if he/she shows no glycosuria. Ray (120) placed his patients into three groups according to the control of diabetes. Those consistently showing no glycosuria were placed in the group of "good" control; those showing traces of glycosuria were classified as "fair", and those showing considerable glycosuria were considered to be in "poor" control.

D. THE PERIODONTIUM

The periodontium is the tissue which surrounds and supports the tooth, it is composed of the gingiva, the periodontal ligament, the cementum on the root surfaces and the alveolar bone. The periodontium is considered a functional biological unit (65).

The Gingiva.

Anatomically, the gingiva is divided into two parts - the free and attached gingiva. The free gingiva extends from the dento-gingival junction to the dental groove and interdentally forms the gingival papilla. The dental groove, which is often absent is a line on the facial surface which corresponds to the location of the bottom of the gingival crevice. The gingival crevice or sulcus is the groove around the tooth, formed on one side by tooth surface and on the other by epithelium lining the free gingival margin. The base of the crevice is the coronal part of the epithelial attachment to the tooth surface, and the depth of the crevice varies from zero to several millimetres (65).

The attached gingiva extends from the free gingival groove to the mucogingival junction and covers cementum of the tooth and alveolar bone.

Normally gingiva is firmly attached to the under-

lying bone; interdentally, the free gingiva constitutes the gingival papilla. The interdental gingiva may consist of two papillae, one buccal or labial and one lingual or palatal to the tooth contact area - that is, the interdental gingival margin has the appearance of a col (65a) (119). The gingival margin should end in a knife-edge and be scalloped mesio-distally. The gingiva is stippled in appearance except on the margin border and on the interdental papillary margin. It is composed of epithelium and connective tissue.

The Epithelium.

The gingival epithelium is of the stratified squamous type. The epithelium lining the free and attached gingiva is keratinised except for that part which lines the gingival crevice (119). Gingival epithelium may be separated histologically into several cell layers (119):

1. The basal cell layer
2. the stratum spinosum
3. the stratum granulosum
4. the stratum corneum

as the cells move from layer 1 to layer 4, the metabolic activity would seem to decrease and degeneration to increase.

Recent studies have shown that the structure holding

epithelium cells together is the desmosome (65). The desmosomes remain intact throughout the passage of the cell from the basal layer to the surface, they appear to keratinise along with the rest of the cell and when they rupture the cell is shed (119). There may be other intercellular substances which take part in cellular adhesion but as yet little is known of these substances.

Epithelium cell regeneration.

Superficial epithelial cells are being continually desquamated, so that the surface layer must be constantly added to by the formation of cells from lower layers. It is generally agreed that cell regeneration takes place from the basal and spinosum layers and that the renewal of epithelium takes place by mitotic division in these cell layers (119).

A number of factors are known to increase mitotic activity. (119)

- a. removal of superficial keratin
- b. increased oxygen tension
- c. increased glucose levels of the blood.

Epithelium also responds to inflammation in the underlying tissue with increased mitotic activity, unless secondary changes within the epithelium interfere with cell division - this may be an unspecific response to

increase of the circulatory supply, however, it has also been suggested that the inflammatory cells may provide factors which stimulate the rate of mitosis. Induction of hypoglycaemia with insulin, however depresses mitotic activity (119). Cortisone has been shown to exert a similar effect. Insulin has been shown in animal studies to cause hyperplasia and hyperkeratinisation of the epithelium covering the gingiva (35).

In order to carry out their normal functions, cells have to be provided with energy as well as with a number of substances required for the synthesis of their component parts. Nutrition is concerned with supplying energy and the building blocks utilised for synthesis. It would appear, that in epithelial keratinisation it is aerobic glycolysis which is the most important manner of providing energy (119).

An aspect of carbohydrate metabolism in the gingival epithelium which has been studied is the occurrence and fluctuations of glycogen. In the clinically normal tissue the amounts of glycogen present within the cells are small, although some cells of the outer spinous layer at the free gingival margin regularly contain glycogen. When gingivitis is clinically manifest, the amounts of glycogen demonstrable are greatly increased

(119). In the epithelium of the skin increased amounts of glycogen accumulate in the pathological states associated with tissue damage and repair. Thus, glycogen is prominent in the epithelium in connection with inflammation as well as when there is increased epidermal proliferation (119). A controlled injury of epithelium by stripping off layers of tissue with scotch tape demonstrated accumulation of glycogen eight hours following the injury. After forty-eight hours glycogen was no longer present; however, seventy-two hours after injury there was a new wave of glycogen deposition within the cells of the stratum spinosum. In the course of a week the glycogen disappeared. It has been suggested from these facts that the accumulation of glycogen within the epithelial cells is due to a reduced metabolic rate because of injury (119).

Glucose which is not immediately metabolized by the cell is converted into glycogen which represents an important store of energy. When epithelial cells are in active mitosis and keratinise rapidly no glycogen accumulates. (119). This is commonly considered to mean that glycogen is metabolised for the production of energy, instead of being stored. Hence glycogen would be expected to accumulate within injured cells when their

metabolism is impaired. That is the amount of glycogen present in keratinising epithelium might represent an index of epithelial metabolic activity (119).

Keratinisation.

The process of keratinisation includes the transformation of cytoplasmic proteins into keratin filaments, as well as the complete disintegration of the keratinising cell, in the sense that both the cytoplasm and the nucleus become decomposed (119).

The relation of glycogen to keratinisation has been subject to much speculation. It is possible that glycogen serves as a source of energy for keratin formation (119). This assumption is based on observations to the effect that the factors which suppress glycogen synthesis also reduce the mitotic activity of epithelial cells, and a reduced mitotic activity involves a decreased rate of keratinisation. In animal experiments dealing with wound healing in skin it has been found that with the onset of epithelialisation, the new epithelial cells contain much glycogen (119). Glycogen is present in the outer parts not in the basal layers. As the outer cells start to keratinise they lose their glycogen. This has been interpreted as follows:-

The new epithelium, being relatively far from the blood

vessels, has a poor oxygen supply. Therefore, the cells have to operate through anaerobic glycolysis. As they leave the basal layer, the cells start to store glycogen which is later used to supply energy for the synthesis of keratin. By the time keratinisation is completed, all of the glycogen has been used (119).

These observations show the strong possibility that glycogen plays a major part in the keratinisation of gingival epithelium, and therefore any factor that interferes with the supply of glycogen to the tissues must have deleterious effects on this protective layer (119).

Histologically, keratinisation in the marginal epithelium varies from little tendency to keratinisation, through more or less complete parakeratosis to full keratinisation. The surface layer of the marginal epithelium appears to be parakeratotic in most cases rather than exhibiting the typical non-nucleated keratinisation of skin (65).

Parakeratosis is characterised by the retention of cell nuclei in the superficial layer of the epithelium. It has been suggested that parakeratosis is the result of accelerated proliferation. When more cells than normal are formed per unit time, keratinisation must proceed faster. Such an accelerated keratinisation

becomes incomplete, as evidenced by the retention of nuclear structures and seemingly more or less by-passing of the granular stage (119).

Dento-gingival Junction.

The area of contact between the gingival epithelium and the tooth surface is unique in the human body.

Glickman (58a) stated that the epithelial attachment consists of stratified squamous epithelium which is three to four layers thick in early life but increases up to 10 to 20 layers with age. Grant, Stern and Everett (65a) state that the epithelium attachment appears to be composed of an epithelium that differs somewhat from the gingival epithelium. On the enamel this epithelium may be composed of reduced ameloblasts, whereas on the cementum this epithelium may be originally derived from the stratum medium of the enamel organ. They also contend that these epithelium cells do not keratinise, and that the junction of the epithelium attachment and the connective tissue usually forms a smooth surface without penetration of connective tissue papillae.

Stern (65a) stated that when viewed in the electron microscope, the cells of the epithelial attachment appear to attach to the tooth by a system of hemidesmosomes. However Shultz-Haut (138a) states that considering the

biology of the epithelial attachment, it appears unlikely that a fixed, structural-organic attachment of these cells to tooth structure could exist. The epithelium is constantly renewed by cell division in the basal layers, accompanied by a gradual migration to the surface of older cells and a desquamation of the superficial ones. These facts, Schultz-Hauidt (138a) contends have led to the proposal that the epithelial cells are held in contact with the tooth surface by physico-chemical forces of adhesion.

The Connective Tissue.

The connective tissue consists of cells, fibres and vessels embedded in a viscous ground substance. The cells are mesenchymal cells, fibroblasts, mast cells and macrophages. The fibres are of the collagen, and reticular type and some elastic types. (119)

The components of the connective tissue inter-cellular matrix is derived from blood, parenchymal cells and connective tissue cells. One main locally produced component is the glycoprotein. The carbohydrate of the glycoprotein is built from glucose, galactose, mannose and fucose, and smaller amounts of other sugars (119).

Many of the important functions of the connective tissue are directly related to the ground substance

because it constitutes the actual environment of most cells, moreover, the ground substance is of great importance in the protection of the organism against bacterial invasion, as well as against certain forms of trauma (119).

At the present time it is difficult to ascribe any particular or specific physiological function to the glycoproteins of the ground substance, they may in some way be related to fibre formation. It has also been pointed out that they can influence contact interrelations between cell surfaces (119).

Some hormones appear to act on the connective tissue proper. An interference with the synthesis of acid mucopolysaccharides results in altered connective tissue physiology, and this may, in turn, modify tissue resistance, and this may be the basis for the clinical observations that diabetes is regularly accompanied by periodontal disease (119).

The Periodontal Ligament.

The periodontal ligament is the sheet of connective tissue which is situated between the cementum covering the root of the teeth, and the alveolar bone. It is continuous with the connective tissue of the gingiva and communicates through vascular channels in the bone and

narrow spaces. The main functions of the periodontal ligament is to transmit the occlusal forces upon the teeth to the alveolar bone, and to act as a cushion to the impact of these forces (119).

The periodontal ligament also has a formative function. Glickman (58a), Grant, Stern and Everett (65b), Sicher (147a) and Schultz Haudt (138a) state that osteoblasts and cementoblasts derived from the ligament are concerned in the formation of bone and cementum. It is in this manner that the periodontal ligament acts as periosteum to the two calcified tissues. Glickman (58a) also states that cells which are associated with the resorption of bone and cementum are also derived from the ligament.

The morphology, chemistry and metabolism of the periodontal ligament elements must be similar to those of the same elements of connective tissues in general.

The Bone.

The alveolar bone consists of two boundary plates of cortical bone, between which there is a network of cancellous bone. This is filled in by bone marrow, blood vessels and nerve fibres. Into the bone plate which lines the dental alveolus numerous bundles of collagen fibres from the periodontal ligament are inserted.

These fibres are referred to as Sharpey's fibres, and an area of bone containing a large number of Sharpey's fibres is called bundle bone (119).

Bone is a type of connective tissue. It is composed from cells and an intercellular matrix which is more or less calcified. There are considerable variations in the composition of bone depending upon its degree of maturation. On the average, about sixty per cent of dry bone is inorganic and forty per cent is organic. The water content varies between fourteen and forty per cent - this is much less than in the majority of the tissues (119).

Histologically, the first sign of bone formation is the appearance of osteoid. Osteoid is considered at the present moment to be formed by the osteoblasts. Bone is then deposited in this matrix. One of the most prominent enzymes in osteoblasts is alkaline phosphatase which is always present during calcification of bone (119). Glycogen is assumed to have a function in the formation of the substrates for alkaline phosphates - this theory is strengthened by the observation that glycogen largely disappears during the transformation of an osteoblast into an osteocyte (119).

Cementum.

Cementum is defined as the calcified mesenchymal

tissue which covers the anatomic root of the tooth. The major function of the cementum is to secure an anchorage of the tooth. The attachment is provided by collagen fibres from the periodontal ligament which in the form of Sharpey's fibres, are embedded into the cementum. Alkaline phosphatase has been noted in the metabolism of cementoblasts and cementocytes (119).

Discussion.

From this brief study of the periodontium, and the apparent part glycogen plays in all its tissue constituents, and especially the part it appears to play in the keratinisation of epithelium (a very important defence mechanism), one is presented with the obvious fact that any disease which interferes with the supply of this all important substance must lower the vitality of the periodontal tissue. Diabetes mellitus interferes with the supply of glycogen to the peripheral tissues, and, therefore must be suspect when periodontal disease is present in a diabetic patient, but only a great deal of research, epidemiologically, histologically and biochemically will prove or disprove this point.

E. PERIODONTAL DISEASE

Gingivitis is an inflammation of gingiva, the outstanding clinical changes of gingivitis are inflammation (changes in tissue colour and form) and haemorrhage. The inflammation may be acute or more often, chronic and the clinical features may include hyperplasia, ulceration, necrosis, formation of pseudomembranes and purulent and serous exudation. The lesions may be localised or generalised and may be distributed in the papillary, marginal or attached gingiva (65).

Periodontitis is an inflammatory disease of the gingiva and of the deeper tissues of the periodontium. It is characterised by pocket formation and bone destruction. (65). Periodontitis is considered a direct extension of gingivitis that has advanced and has been neglected. The difference between gingivitis and periodontitis is "quantitative rather than qualitative" (65). Periodontitis is caused primarily by local irritational factors and may be complicated by systemic diseases, endocrine disturbances, nutritional deficiencies, or other factors (65). Whenever the inflammatory process of the gingiva extends into the deeper supporting tissues and part of the supporting apparatus has been destroyed, a diagnosis of periodontitis can be made. One of the

characteristic findings in periodontitis is the periodontal pocket. The extent of the pocket depth in periodontitis is not due to enlargement and swelling of the gingival margin, but rather to progressive pocket encroachment on the periodontal ligament. The clinical diagnosis of periodontitis is based on obvious gingival inflammation, pocket formation and alveolar resorption. Mobility may be a late symptom, and sometimes is minimal, even after extensive alveolar bone loss (65).

F. PERIODONTAL DISEASE IN DIABETES MELLITUS

The relationship of diabetes to periodontal disease has been suggested repeatedly in the literature, but there is little unanimity of opinion regarding the nature of the relationship. Rutledge (132) in 1940 studying a group of twenty patients between the ages of eight to nineteen years showed frequent and definite signs of gingivitis and periodontitis. Whether these patients were well controlled is not stated in the study, and unfortunately no control patients were studied. Therefore the study merely shows that a number of twenty patients studied had diabetes and periodontal disease. On the other hand Sheppard (143) in 1942 studied a group of one hundred diabetic patients and found none of the extensive signs and symptoms of "pyorrhea" described in the literature, when there were signs and symptoms he ascribed these to patients age. Sheppard used no controls and stated in criticism of his article "the evaluation of findings under the heading of "pyorrhea" were found to be difficult". Rudy and Cohen (125) in the same year studied eighteen diabetic patients and stated that the adult medically controlled patients have a high incidence of marginal type of periodontitis due to calcular deposits and lack of oral hygiene. This was not a controlled

study, the number of adult patients was small (five) and the method of recording periodontal disease was, to say the least, unrefined.

Lovesdalt and Austin (91) in 1943 completed a study of five hundred and three diabetic patients and one thousand and twenty-three patients as controls, sex and age were the fixed variables in this study. The conclusions they arrived at were that advanced periodontal disease occurred more frequently in diabetic patients, however their manner of "grading" periodontal disease was limited and only recorded gross differences. In the same year Schour and Hassler (137) stated that most investigators reported no abnormal findings in the periodontal tissues of fully controlled or partially controlled diabetics. Unfortunately they gave no references for this statement.

Ziskin, Siegel and Loughlin (170) in 1944 studied ninety-four juvenile diabetics and stated that owing to the consistent and striking nature of the gingival colour changes, some element relating to diabetes, as yet obscure, probably acts as an influential causative factor. The same year Ziskin and his group (169) carried out a histological study on a small number of patients (namely nineteen), and were able to show hyperkeratinisation,

hyperplasia of the epithelium and connective tissue, increased glycogen deposition, increase of fibroblasts and prominence of the capillary bed, and a reduction of inflammatory exudate in the corium of insulin treated patients, but not in diet controlled patients. The absence of controls in both studies and the small number of patients in the latter unfortunately limit their value.

Glickman (58) in 1946 studying animals with Alloxan-induced diabetes found no specific changes in the gingival tissues. He stated that even though consideration must be given to the limitations which govern the validity of correlations between findings in animal experiments and disease as it occurs in humans, there are facts which can be offered with regard to periodontal disease in human diabetes:-

1. In individual patients, diabetes is not responsible for specific gingival changes or for the onset of gingival disease.
2. A tendency towards "periodontoclasia" which has a systemic origin may result in a loss of tooth supporting bone, even with the absence of gingival changes in a large percentage of diabetic patients.

3. The progress of "periodontoclasia" in individual diabetic patients in whom the alveolar bone is affected by generalised osteoporotic changes may expectedly be more rapid than that which would occur in the absence of diabetes.
4. "Periodontoclasia" in diabetic individuals presents no specific microscopic features which warrant its designation as a unique clinical entity.

At the present time it is universally believed that the condition known as diabetes mellitus is present in a prediabetic or subclinical form long before a diagnosis is made and that many changes have occurred in the tissues before the final diagnosis. As Alloxan induces a diabetic-like state without this long term prediabetic struggle, the studies of Alloxan-induced diabetic animals must be viewed with reservations.

Pollack, Porson and Knishkoy (116) in 1947 state that the diabetic is subject to all the lesions found in the non-diabetic, however their gross appearance may be altered because of the presence of diabetes, but the underlying pathology is the same. The lesions will vary, they stated, with the state of control of diabetes, with the age of the patient, with the duration of diabetes,

with the cause of diabetes and with any other nutritional or metabolic condition.

They offered an explanation for the rapid bone change in certain types of diabetes. The acute and uncontrolled diabetic is usually in a negative nitrogen balance which means there is a drainage of the body proteins. Calcium metabolism and transport through the blood are dependent upon an adequate protein metabolism. Thus it is conceivable that with depleted proteins, there is a breakdown in the balance between bone formation and bone resorption. This same disturbance in the protein metabolism of the diabetic may explain his susceptibility to infection. It is known that immune bodies in the blood are in the gamma globulin. In starvation and diabetes, the gamma globulin may disappear from the blood and hence the loss of resistance to infection.

Harbo (96) in 1947 contended that arteriosclerosis with its sequel has become the major complication of diabetes. The findings in his study of two thousand one hundred and ninety-one patients were that seventy per cent of diabetic patients have definite evidence of arteriosclerosis after twenty years of diabetes and that where control of diabetes is not complete there is an increase in capillary fragility. Amos and Parks (3)

in 1948 in a study of thirty-two diabetics between the ages of six and fourteen years, found the gingival condition was "only fair or frankly poor", salivary calculus was generally present, but alveolar bone resorption was not present radiographically, no controls were used in their study so that their findings need to be proved in a more objective study.

In a histopathological study of the gingival tissue of thirty diabetic patients, Ray (120) in 1948 found a chronic inflammatory reaction characterised by the accumulation of plasma cells and lymphocytes. The lymphocytes were often localised in the papillary layer and invaded the epithelium; the lymphocytic infiltration was independent of any inflammation in the periodontal pocket. Ray (120) felt that the diabetic state modified the relation of the gingival tissues, partly by inducing an early vascular damage. In the same year Stahl (151) published an article in which he reported that after a clinical examination and full mouth roentgenographs of fifty-six diabetic patients and after bacteriological tests of a further thirty-eight diabetics, he found that with an increase in the severity of the diabetic state there is an increase in the roentgenographic and gingival changes in most cases, and that haemolytic staphylococcus

can be isolated more frequently from the saliva of diabetic individuals. Roy (120) gave no detailed figures to support his observations and neither Roy (120) nor Stahl (151) used controls.

Golomb (61) in 1949 in an article emphasises that studies should state whether controlled or uncontrolled diabetics are being examined. After a review of the literature Golomb concluded that commonly described periodontal lesions seen in diabetic patients appear to be secondary to local causative factors.

Roy and Orban (121) in 1950 in an investigation based on clinical and histological examination of the gingiva of seventy-six patients, thirty-six of whom were diabetics and the remaining forty were in good physical health, stated that the severity of gingivitis appeared to be accentuated in the diabetic patients and would seem to represent an increased tissue reaction to local irritation. Stahl, Wisan and Miller (152) in 1952 in a study of three hundred hospital patients stated that disturbances in metabolism such as diabetes may handicap tissue, including periodontal tissues, in maintaining normal function. Under these conditions, periodontal disease may develop and run a rapid course even though local causative factors were minimal. They emphasise

the close correlation between the severity of periodontal disease and age. Swenson (156) in 1954 outlined a case history in which he showed gross alveolar bone resorption in an uncontrolled diabetic patient. Later in the same year Sandler and Stahl (133) in a study of one thousand two hundred and ninety-nine white hospitalised veterans supported the hypothesis that generalised diseases tend to influence the initiation and increase the severity of periodontal disease. The scoring of periodontal disease in this study is the author's own and is not comparable with other studies or easily reproduced. In 1954 another article of interest appeared written by Person (115) in which he discusses bone resorption, he pointed out that the local factors in two cases he presented were not sufficient to cause the severity of bone resorption and that uncontrolled or poorly controlled diabetes in these cases with its negative nitrogen balance must be a strong causative factor.

Goldman and Cohen (60) in 1957 stated that examination of the periodontium of diabetic patients revealed many cases unaffected, but also many that showed marked destructive changes in the periodontium which they contended was not responsive to treatment. They

concluded that once the diabetic process gains a foothold, a cause and effect relationship ensues. Healing is below par because of the diabetic state and the periodontal manifestations become exaggerated. Sindoni (148) in a report written in 1958 points out that dentists should be aware of the increased incidence of oral disorders in diabetics and contends that this is due to the generalised vascular complications of diabetes which must, he contends, be found in the oral cavity.

Before discussing a series of papers which describe research carried out at the University of Alabama, the glucose tolerance test for the diagnosis of diabetes will be described. Mosenthal and Barry (107) in 1950 published a set of values which are now generally regarded as the normal glucose tolerance pattern. They suggest that the normal glucose tolerance is represented by a fasting venous glucose level of 100 or less milligrams per cent, no venous glucose level greater than 150 milligrams per cent and a return of the blood glucose level to 100 or less milligrams per cent at the end of two hours. Individuals showing a decrease in glucose tolerance as evidenced by a blood glucose level of 150 or more milligrams per cent during the three hour test and a failure to return to below 100 milligrams per cent at the two hour period, are

regarded as suffering with diabetes mellitus by many investigators. Individuals characterised by a mild decrease in glucose tolerance, as evidenced by a rise in true glucose level to above 150 milligram per cent or a failure to return to below 100 milligram per cent at the two hour period are regarded by some investigators as suffering from prediabetes mellitus.

Sheridan and his co-workers (145) in 1959 wrote the first of this series of studies which will be discussed. In one hundred routine dental patients which this group studied, a highly significant number; namely twenty-six showed evidence of decreased carbohydrate tolerance, whether all or some of these individuals should be regarded as diabetic is basically a definition of the term diabetes mellitus. They stated that of these patients who showed extremes of glucose tolerance increased or decreased, the majority were of the female sex, but considering that seventy-eight patients out of the hundred patients examined were female, this fact must be viewed with great reservation. This group stated that every patient who reported with a primary admission complaint of loose teeth also demonstrated a decreased glucose tolerance. In this study a negative family history of diabetes mellitus proved of little help in eliminating the possibility of

decreased glucose tolerance and possible diabetes mellitus. The group further showed that intraoral symptoms proved quite helpful in the detection of possible diabetes mellitus. Dry and burning mouth, gingival tenderness and pain with tooth percussion occurred more frequently in patients with decreased glucose tolerance and that some of the intraoral signs (lip dryness, severe loss of gingival stippling, so called spontaneous gingival bleeding, marked changes in gingival hue, absolute pocket formation. Increased P.M.A. index, tongue colour, tooth mobility and loss, and presence of calculus), occurred with greater frequency in those patients showing evidence of decreased glucose tolerance. Added to these findings the roentgenographs which showed alveolar bone loss and marginal widening of the periodontal membrane were more often those of patients with confirmed or possible diabetes mellitus.

The next study in this series was reported by Choraskin and his co-workers (31) in April 1960. In this study an analysis of the normal glucose tolerance is made with regard to the absence or presence of oral symptoms which are commonly associated with diabetes mellitus and the following statements were their conclusions:-
If judged by the standards of glucose tolerance estab-

lished by Mosenthal and Barry (107) the one hundred patients examined appeared normal but if the glucose tolerance was judged at the second hour, the one hundred patients would be regarded as systemically abnormal. This study showed burning mouth, rather than xerostomia and gingival tenderness appeared to be more related to diabetes mellitus. Patients who suffered xerostomia, stomatopyrosis and gingival tenderness appeared to be more likely diabetics than the patients who suffered from merely one or two of these complaints. Age did not appear to play a role in the relationship of oral symptoms to glucose tolerance pattern. However a low number of patients were used to derive these conclusions and therefore they are of limited value.

Reporting another study Choraskin, Brunson and Goodwin (32) in July 1960 stated that the combination of polyphagia, polyuria and polydipsia are more representative of a disturbance in glucose metabolism than is the triad of oral symptoms, namely xerostomia, stomatopyrosis and gingival tenderness. But they contend the pattern of oral and extraoral symptoms are essentially the same. Therefore it appears that the oral symptoms can be used to distinguish normal and abnormal tolerance patterns, moreover the patterns

derived from the intra-oral symptoms are more delicate indices of the glucose tolerance pattern.

If it is possible to reproduce and confirm the findings in these last three studies, further aids to the diagnosis of diabetes and the detection of the prediabetes will have been discovered.

Burket and Sindoni (59) in 1959 in an article state that the blood vessels of diabetics are often unusually fragile and that the greater susceptibility of the tissue even in the controlled diabetic is strong motivation for improved prophylaxis in patients suffering from this disease. Faird (6) in 1960 studied a group of eighty-seven patients (fifty-three of whom were edentulous) suffering from diabetes mellitus and found no characteristic gingival or periodontal lesions in the well controlled diabetic. Faird outlined a very thorough method of scoring periodontal disease, the method is very similar to Russell's periodontal index (126) but involves greater charting detail which limit its use in large epidemiological studies. The study continues to discuss eight cases showing clinical periodontal disease associated with a flat glucose tolerance curve - these patients Faird considered were probably prediabetics. Here again in this study no controls were used and only a small number of

patients were examined the survey was more an exercise in the use of a periodontal index than a study of periodontal disease in diabetics and so no definite conclusions as regard the incidence and severity of periodontal disease in diabetics can be derived from his study.

Sandler and Stahl (154) in 1960 examined three thousand nine hundred and ninety-four hospitalised patients between the ages of twenty and sixty-nine years. They concluded that the influence of generalised disease upon periodontal health was not remarkable except in patients with relatively severe diabetes and in those with cirrhosis of the liver (who were usually alcoholics). Their survey also showed higher periodontal disease scores in patients with atherosclerosis and gastro-intestinal disorders, but the increase in periodontal disease in these last two disorders was not great enough to be significant.

Williams and Mahan (164) in 1960 studied a small group (nine) of young diabetic patients ranging in age from twenty to thirty-two years and formed the conclusion that gingival and periodontal disease is common in young diabetic patients. This study can only express an opinion as regards the patients examined for no controls were used nor was the method of scoring periodontal disease explained.

In 1962 Shklar, Cohen and Yorganian (146) studied a

group of twenty Chinese hamsters with hereditary diabetes and showed that severe periodontal disease was present in the diabetic animal, they used controls for this study, and stated that the Chinese hamster is an excellent animal for the study of periodontal pathology in the diabetic state. The hereditary diabetes mellitus in this strain of animals corresponds very closely to human diabetes. Even when the limitations with which animal studies can be applied to determining the course of a disease in human beings is considered and that the manner of scoring periodontal disease was not explained, this study must give support to the idea that there is a strong correlation between diabetes mellitus and periodontal disease. Hereditary diabetic hamsters were also studied by Cohen, Shklar and Yerganian (35) during 1963, when they observed striking periodontal alterations in the diabetic animals in contrast to conditions in the control animals. These alterations consisted of calculus - like deposits on the teeth, migration of the epithelial attachment, splitting of the epithelial attachment, and pocket formation, alveolar resorption and extensive inflammatory infiltration. All the diabetic animals in this study presented some variations from normal ranging in degree of mild gingival inflammation and epithelial hyperplasia to severe periodontal pocket

formation with alveolar bone resorption.

Cottsoy (63) in 1962 reviewed the literature on oral considerations in diabetes mellitus and stated that gingival inflammation and infection seem to be more severe in the uncontrolled diabetic patient than in either the controlled diabetic patient or the non-diabetic patient. This he contended may be related to a lowered resistance to infection in the uncontrolled diabetic. Cottsoy also stated that between the ages of eighteen and forty years diabetic individuals manifest a higher incidence of severe periodontal bone resorption than can be attributed to local causes alone, but that below the age of eighteen years diabetics show no premature alveolar bone resorption.

In 1962 Kerr (81) stated that if the nature of periodontal disease is considered as a chronic destructive process of the periodontium, which progresses at various rates, depending on the individual's ability to repair the damaged tissue, one would expect the progress to be more rapid in any condition which influences repair. Protein deficiency is known to delay repair; therefore in individuals 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. As a number of authors (116) (113) have stated that diabetes causes a drainage of body proteins, Korr (61) infers increased severity of periodontal disease in diabetic patients. Korr contended, however, that it has never been demonstrated that periodontal disease can be initiated by means of dietary deficiency.

In a two part study O'Leary, Shannon and Prigmore (110) in 1962 showed in the first part strong correlation between calculus and plaque to periodontal disease, after comparing fifty-nine patients with periodontal disease and a control group of sixty-four "nondiseased" patients. In the second part they studied twenty patients with gingival or periodontal breakdown to evaluate their carbohydrate metabolism by employing the intravenous glucose tolerance procedure. One of the patients studied showed a decreased carbohydrate metabolism which suggested a mild diabetes mellitus. They explained that the oral glucose tolerance test is dependent on the gastric emptying rate and the rate of intestinal absorption and that the test is therefore weakened by these two facts, and the results obtained are subject to question except in the diagnosis of frank diabetes mellitus. The reproducibility of the intravenous glucose tolerance procedure is a definite

advantage in carrying out comparative studies. These authors found no valid correlation between gingival and periodontal status and carbohydrate metabolism when they used either an oral glucose tolerance test or an intravenous glucose tolerance procedure. This study merely demonstrates that periodontal disease occurs in individuals without decreased carbohydrate metabolism.

Stahl, Witkin and Scopp (154) in 1962 after studying gingival biopsies of eighteen hospitalised patients suffering from diabetes mellitus concluded that the gingival vascular bed mirrors rather accurately the generalised vascular state of the diabetic patient and postulated that this may be at least partially responsible for the increased periodontal disease observed clinically in patients suffering from diabetes. Their theory was further emphasised when they failed to find similar vascular changes in the control group.

In 1963 Mackenzie and Millard (95) studied sixty diabetic patients, sixty-four patients suspected of being diabetic and fifty-four arteriosclerotic non-diabetic patients and concluded that although a relation between arteriosclerosis and diabetes mellitus was demonstrated, a positive influence of arteriosclerosis on alveolar bone loss in diabetes mellitus was not found, but there was a

high positive relation between calculus and alveolar bone loss. Exactly how the amount of calculus was recorded for comparison is not described. They also stated that an increased amount of calculus in people with diabetes is either small or non-existent and that diabetes affected neither the amount nor pattern of bone loss. The patients studied in this survey were from a high socio-educational group and according to other surveys (24) (89) (104) (105) (128) (129) (153) would tend to show lower periodontal disease than the average patients, and as the current thought is that diabetes affects the severity and progress of periodontal disease when present, rather than the incidence, the group of patients studied are unsuitable and do not represent a true random study.

Rose, Kuna and Kraft (124) in 1963 using the serum of twenty-four patients with periodontal disease and fifteen patients showing no periodontal disease to determine the amount of calcium, phosphorus, sodium, potassium and alkaline phosphatase and having roentgenograms taken of the patients' left or right elbows, came to the conclusion that periodontal disease seemed to be a combination of two factors, one local and the other systemic. The local factor causes irritation to the periodontium and the systemic

factor interferes with the supply of building materials necessary to repair the injured area. The authors of this article suggest that high blood sugar levels deplete the available body phosphorus and cause a predisposition to bone destruction and therefore consider diabetes mellitus is involved in increasing the severity of periodontal disease.

In 1964, a symposium on diabetes mellitus brought together Choraskin, Gottsogen, Rifkin and Shklar to discuss this condition and its relationship to periodontal disease.

Choraskin (33) presented material on the relationship of the cortisone glucose tolerance test to periodontal disease; he stated that this test is more accurate than the standard glucose tolerance test and should be used when familial history or other findings point to the possibility of the existence of diabetes mellitus. It was his further contention that the hypoglycaemic of today may be the hyperglycaemic of tomorrow, and that patients with subjective gingival tenderness have more significant changes in blood sugar levels than those with no gingival tenderness.

Gottsogen (64) emphasised the concept of "pre-diabetes" playing a part in the aetiology of periodontal

disease and suggested that the possibility of vascular changes causing a breakdown of periodontal structures. These changes he contended may exist before clinical diabetes is evident. He pleaded for periodontists to insist that glucose tolerance tests be done when the treatment of periodontal disease was not successful.

Rifkin (122) discussed clinical diabetes and stated that since the advent of insulin and antibiotics, diabetes has become clinically a disease evidencing uremia, progressive loss of vision and vascular changes rather than acidosis, coma and fulminating infections. He also emphasized the nature of the vascular changes or microangiopathy and described these as microaneurysms similar to gross aneurysms.

Shklar (147) presented the results of experimental work on periodontal disease in the heredity diabetic Chinese hamster and showed these animals to be very susceptible to periodontal disease. The histologic sections he displayed, showed migration of the epithelial attachment, bone resorption and periodontal abscesses.

In their book on disease of the oral mucosa, McCarthy and Shklar (93) in 1964 stated that no oral lesion is specific in nature to a diabetic and terms such as "diabetic stomatitis" should not be used. However, they

continue, that because of the lowered tissue resistance, there is a definite tendency for the development of severe periodontal disease, of periodontal and periapical abscesses and of severe tissue destruction when areas of mucosa become traumatised and infected. These authors contend that in normal children gingivitis is commonly observed particularly at puberty, but that severe periodontal breakdown is a rare finding, however, on the other hand severe periodontal breakdown is seen more often in children with diabetes, and even in a well controlled case the tissue response may be poor.

Glickman (59) in 1964 stated that despite the generalised increased susceptibility to infection and severe inflammation in diabetes, a number of investigators recognise no relationship between diabetes and oral disease and maintain that when the two conditions exist together it is coincidental rather than a specific cause and effect relationship. He states that microscopic changes are unique or characteristic of diabetes and the severity of inflammation is not correlated with the state of control of the diabetes. The basis for these statements would be strongly formulated by Glickman's studies of Alloxan induced diabetic animals, these studies are much more limited in their application to human diabetics than are

the studies of Shklar (146) and Cohen (35) on hereditary diabetic animals because in the latter animals, pre-diabetic struggle and tissue changes are much more likely to have paralleled the condition which is assumed to take place in the human diabetic.

Bolting, Minikoff and Dummett (11) in 1964 studied seventy-eight diabetic patients and an equal number of non-diabetic but chronically ill patients. The facts recorded for both the diabetic and non-diabetic patients were age, degree of calculus, brushing frequency, bruxism and clenching habits. This study showed that in the whole group ranging in age from twenty to eighty-nine years, the mean Russell periodontal score was significantly greater in the diabetic group. Within each ten year age group the thirty to thirty-nine and the forty to forty-nine years were the two groups that showed statistical significance. The study also showed that as the degree of calculus increased the severity of periodontal disease increased significantly in both groups of patients, and that as brushing frequency increased the severity of periodontal disease decreased in both patients, but the decrease was not statistically significant. Perhaps if an oral hygiene index (which includes a debris index besides a true calculus index) had been used instead of a

very basic calculus score and tooth brushing frequency, the results would have given a number of extra facts for consideration. One wonders how effective is the tooth brush technique practised by most patients, and therefore, whether it is worth recording tooth brushing frequency in these studies. The control patients in this study were suffering from mental, circulatory and digestive diseases, and as each of these diseases have been shown by Ebeling and Gupta (10) and Sandler and Stahl (133) (134) to influence the severity of periodontal disease the figures in this study assume even greater significance.

Shannon and Gibson (141) in 1965 carried out a study which compared periodontal status and glucose tolerance in three hundred male patients between the ages of seventeen and twenty-two years, and concluded that there was no indication that periodontal disease was related to glucose tolerance. The age group studied was shown by Ebeling, Hiniker and Dummett (11) to have very low periodontal disease scores both in the healthy and diabetic patients. The highest periodontal disease index is usually shown after forty years of age, which is also the age that most individuals show degenerative vascular changes (2a). As vascular changes occur in diabetics some ten to twelve years earlier, (18) (62) (53a) changes in the periodontal

tissue due to diabetes may be expected to occur somewhere about thirty years of age, and not in the early twenties as studied in this group.

Another study in 1965 was carried out by Choraskin and Ringsdorf (34) of two hundred and ninety patients, one hundred and twenty were subjected to the normal glucose tolerance test and one hundred and seventy were tested by the cortisone glucose tolerance procedure. In this study they stated that gingival pathosis is associated with both hyperglycaemia and hypoglycaemia. In the same year Levine (86) in a short abstract is reported as stating that in diabetes, gingivitis may be acute and the loosening of teeth rapid, and that the susceptibility of diabetic patients to periodontal disease is a common characteristic.

Still in 1965 Hillor and Douglas (101) stated, in a study of sixty-one geriatric patients, that urine sugar analysis is not an adequate means of screening for diabetes mellitus. The test is relatively non-sensitive but is highly specific; usually more than 170 milligrams of glucose per 100 millilitres in whole blood is necessary for a trace of glucose to appear in the urine and if a patient has a high renal threshold more than 240 milligrams of glucose per 100 millilitres of blood can be reached

before glucose is demonstrable in the urine. The glucose tolerance test is the most accurate means available for detecting diabetes mellitus and the urine sugar analysis may be used to control people known to have it.

In 1966 a world workshop in periodontics edited by Renfjord, Korr and Ash (118) reported that more data must be collected before a definite idea can be formed concerning the possible role of general diseases in the etiology of periodontitis, and that only the unfavourable influence of diabetes mellitus seems to be unequivocally established. The committee in this workshop reported that it seems probable that periodontal disease progresses more rapidly in diabetic patients than in individuals free from diabetes mellitus.

Schallhorn (135) in 1966 in a literature review stated that a new concept of diabetes mellitus is that diminished glucose tolerance may represent the end of a hitherto successful battle to resist its developing rather than the beginning of a disease process and that subtle changes may have occurred in small blood vessels prior to the clinical recognition of diabetes. This new concept is helping to unravel many of the previous mysteries of this perplexing disease. In addition this expanded concept offers a partial explanation for the diversity

of findings of investigators relating classical diabetes mellitus to periodontal disease.

Bissada, Schaffer and Lazarov (12) in 1966 carried out a microscopic study on twenty-four rats; twelve had Alloxan-induced diabetes and were kept diabetic for six to nine months before being sacrificed. The other twelve were non-diabetic. The gingival tissue was traumatised in one quadrant of the maxilla of all the rats, with a wire ligature, the opposite quadrant was used as a control. The light microscope evaluation of the periodontal structures in both diabetic and non-diabetic animals showed the following facts:-

1. No specific histopathologic changes were noted in the gingiva or the periodontal ligament of the diabetic animals without local irritation.
2. Nonspecific osteoporosis of the alveolar bone was a characteristic finding in many diabetic animals.
3. Local irritating factors in the non-diabetic control animals caused inflammatory changes in the periodontal structures with epithelial proliferation, pocket formation, and crestal bone resorption.
4. More inflammatory reaction was evident with

marked epithelial proliferation and deeper pocket formation in the diabetic animals with local irritation. Periodontal abscesses were common findings in these animals.

5. The severity of bone loss subjacent to the artificially induced gingival irritation was far greater in the diabetic than in the non-diabetic group.
6. More localised areas of cemental resorption were found in the diabetics with local irritation.
7. Evidence of more thrombosis of the blood vessels of the periodontal ligament was seen in the diabetics.
8. No changes in the capillary and small blood vessel walls of the gingival and periodontal ligament were apparent in the alloxan-diabetic animals at the light microscope level.

Bissada, Schaffer and Lazarow (12) have shown in this animal study that periodontal disease is caused primarily by local causes, that no specific difference existed between periodontal disease in diabetics and non-diabetics, but it was evident that the severity of periodontal disease was much greater in the diabetic animals. The greater difference in the findings of this study and that of

Glickman's (58) in 1941 can be ascribed to the improved equipment which Bissada and his group were able to use, and the fact that they kept their animals in a diabetic state for a much longer period of time.

McMullen (94) in 1967 studied with the light microscope gingival biopsies of five overt diabetics, five chemical diabetics, ten genetic prediabetics and seven normal controls, in this study they showed that four of the five overt diabetics, all of the chemical diabetics and nine of the ten prediabetics had vascular changes within the gingival tissues. One overt diabetic and all the normal controls presented normal gingival vascular morphology. Capillaropathy was more prevalent in the alveolar mucosa; perhaps, they contend, these changes may also be present in the attached gingiva but are minimal and cannot be observed with the light microscope. The capillaropathy was characterised by a P.A.S. (periodic acid schiff) positive thickening of the small vessel walls. The study contended also that capillaropathy did not increase in severity with the increase in the duration of diabetes. McMullen (94) suggests that these studies may present the diabetologists with another diagnostic aid to overcome the frustrating problem of early diagnosis of diabetes mellitus.