

DIABETES MELLITUS.

A study with special reference to its diagnosis and treatment by the general practitioner.

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By

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Introduction.

The success of insulin in the treatment of Diabetes Mellitus is perhaps the greatest triumph in the field of modern therapeutics. With its advent the practitioner has acquired a drug with which to treat successfully a condition which has so many diverse and interesting variations; and he may, with the intelligent co-operation of the patient, face this formidable disease with confidence and optimism.

The main purport of this thesis is to show how the diagnosis and treatment of diabetes and its complications may be carried out by the general practitioner in the most practicable manner.

The thesis has been divided into sections. In the first section a short historical survey of Diabetes Mellitus from its earliest recognition up to the discovery of insulin is given. Following this the etiology of the disease is considered. Theories of causation appearing in current medical literature are examined and a theory concerning the production of the disease is advanced by the writer. The normal and the abnormal metabolism of the carbohydrate, fat and protein foods are then discussed. Diagnosis and prognosis form the contents of the next section.

As the differential diagnosis of the conditions producing glycosuria and of the various types of sugar found is of great importance, special attention is given to this section. Under the fifth section, the treatment of diabetes and of its complications is outlined. This section has been divided into several sub-sections and may be summarised as follows:-

1. Treatment of diabetes in general practice.
2. Treatment of children.
3. Complications which may arise during insulin therapy:- (a) Hypoglycaemia, (b) Haematuria, (c) Eosinophilia, (d) Local skin reactions.
4. Complications of diabetes mellitus and their treatment:- (a) Coma, (b) Pregnancy, (c) Gangrene, (d) Surgical Emergencies (e) Other complications.
5. Cases not responding to insulin-therapy.
6. Insulin substitutes. Synthalin, Glukhorment, Myrtillin, Glucosone etc., etc.
7. Use of insulin in non-diabetic conditions.

Finally a summary of the thesis with the conclusions arrived at is given.

A bibliography is furnished at the end of the thesis.

From the excellent results obtained by the use of insulin it might be thought that diabetes mellitus would figure no longer in statistics as an important cause of death. Examination of official statistics, however, shows that insulin apparently has not decreased the number of deaths from diabetes. An American Bulletin (1) shows that, from reports collected from all parts of the U.S.A., the death rate from diabetes has not been substantially reduced by the advent of insulin. This puzzling situation has been analysed and the following conclusions have been drawn. Firstly that the incidence of diabetes, especially in women, is on the increase. Secondly that insulin does not cure the disease but does prolong life and therefore the gain from death in early life is offset by the loss in later years. And thirdly that the economic prosperity of America has had the tendency to increase the incidence of diabetes. In this country the Registrar-General's statistics (2) show that, although the number of deaths from diabetes has not been materially altered, on an examination of the age at death there is a definite decrease for all

ages except in those over 55. It is probable that the reaction against food-restrictions enforced during the war has led to overfeeding in elderly people, especially in elderly women for the greater increase occurs especially in women over 55.

Rabinowitch (3) has found in Canada that, from calculations of the "known" and "assumed" cases of diabetes, there is a decrease in the mortality rate for all ages. Petren (4) shows from his statistics that in Holland and Sweden the incidence of diabetes for all ages below 50 is on the increase and the mortality rate on the decrease and that both the incidence and mortality rate are on the increase in those over 50. Maclean (5) points out that the cause of death in many cases of those over 55 has probably not been due directly to diabetes, but that, as a glycosuria was present, a return of death from diabetes mellitus was made. It is known that insulin is not so effective in the treatment of coma in the elderly as it is in the young because of the very detrimental effect of this condition to the heart, and it is not unusual for the elderly patient to recover from coma but die from heart failure.

A case of diabetic coma occurring in a patient aged 76 was met with in practice in February 1927. He was treated as outlined under Treatment of Coma and though he was brought out of his comatose condition he died within eighteen hours from heart failure. This patient was seen for the first time when coma supervened but an antecedent history of "heart trouble" was obtained and there were signs of a dilated heart, enlarged liver and oedema of the legs present. Labbé (6) points out that not only is coma detrimental to an already damaged heart but that cardiac collapse may occur during coma in a patient who has had no previous signs of cardiac insufficiency. This type of collapse is due to a vascular hypotension produced by the inhibition of the bulbar vasomotor centre due to the presence of ketosis. He points out that there is an absence of cardiac dilatation and of peripheral or visceral stasis in these cases. This is dealt with further under Treatment of Coma.

From statistics in general it appears that the incidence of diabetes mellitus is on the increase and insulin may therefore take the credit of maintaining the mortality rate of pre-insulin days.

Joslin (7) shows that in the Massachusetts General Hospital the mortality rate of diabetes for all ages dropped from 67.5% in 1922 to 17.8% in 1928. This is a striking tribute to the efficacy of insulin.

Historical Survey.

The earliest allusion to diabetes mellitus which can be found in literature is contained in one of the Brahmimical text books, the Susruta, (8) written in the year 1500 B.C. Here diabetes is recognised as a condition in which "honey-urine" is found and the symptoms of thirst, foul breath and langour are noted. During the Jewish period, about the year 1000 A.D. Avicenna (9) gives a good description of diabetes in which thirst, hunger, polyuria and the sweetish taste of the urine are given. About the year 1670, an Englishman called Willis (10) noted the sweetish taste of diabetic urine and established this basic principle for the diagnosis between diabetes mellitus and diabetes insipidus. Later, in the year 1776, Dobson, (11) another English physician, proved that the sweetness of the urine and of the blood serum was due to sugar. This was the first time that the presence of sugar in diabetic urine and blood serum was definitely established. Following this Peters (12) in 1857 ascertained the presence of acetone in severe cases of diabetes and seventeen years later Kussmaul (13) demonstrated the presence of oxybutyric acid.

In the year 1889 Mering and Minkowski (14) first produced experimental diabetes by extirpating the pancreas and they thus proved a direct relationship between the pancreas and diabetes. They found that partial removal of the pancreas might or might not produce diabetes but that complete extirpation was followed in every case by intense symptoms and fatal termination. Subsequently they found that as little as one fifth of the gland was sufficient to protect from diabetes. This work of Mering and Minkowski was the most important experimental evidence concerning the knowledge of the significance of the pancreas for carbohydrate metabolism which was made up to the discovery of insulin, although the idea of associating the pancreas with glycosuria was of a much earlier date. Thus Brunner (15) in the seventeenth century had attempted to prove a relationship while Bright (16) early in the nineteenth century, exhibited a specimen to show the relationship between pancreatic fibrosis and diabetes mellitus.

Following this work of Mering and Minkowski, Laquesse (17) showed that ligation of the pancreatic duct, although causing an atrophy of the pancreas,

did not produce glycosuria and he thus showed that the anti-diabetic function of the pancreas must lie in its internal secretion.

Opie (18) was one of the first to suggest that this function might lie in the islets of Langerhans (demonstrated by the histologist Langerhans (19) in 1869) and later Ssobolew (20) obtained evidence that animals did not become diabetic when the acinous tissue of the pancreas degenerated but that when the islets of Langerhans degenerated they did; and weight of evidence pointed to there being an internal secretion of this portion of the parenchymatous tissue of the pancreas. Following this a great amount of knowledge concerning carbohydrate metabolism accumulated and dietetic treatment for diabetics was highly developed, especially by Allen. In 1907 the presence of two essentially different types of cells in the islets of Langerhans tissue was established by Bensley and Lane (21) and these types were designated by them as alpha and beta cells. Since then a third type, the gamma cell, has been described. Later it was observed that only the beta cells underwent degeneration in partial depancreatisation, the

alpha and gamma cells remaining in their original form and Allen (22) demonstrated that this hydropic degeneration of the beta cells, occurring in partially depancreatized animals, was caused by an excess of carbohydrate food in the diet. When the animals were fed on a low diet they maintained good health and showed no signs of diabetes and the beta cells showed no degeneration. Allen further found that it was not enough to limit the carbohydrate intake and to allow large quantities of fat and protein to be given as such diets invariably gave rise to diabetes. He found that the correct diet to maintain health was to give the minimum amount of food necessary for the animals' maintenance. From these observations Allen showed that the correct treatment for human diabetics was to give the minimum of food necessary for existence and it is on this principle that the modern treatment of diabetes is based. Many attempts were made by research workers to isolate this anti-diabetic substance from the pancreas. In 1905 Rennie and Fraser (23) prepared an active substance from the islets of certain teleostean fishes and in 1908 Zuelzer (14) obtained a pancreatic preparation

with which he benefited cases of diabetes mellitus and revived some comatose patients. These researches however were abandoned owing to the severe local reaction following injection due to the presence of protein in the preparations, although Zuelzer rendered his preparations fairly free from proteins by precipitation with alcohol.

In the year 1920 Banting (25) conceived the original idea of ligaturing the pancreatic ducts of dogs, waiting for six weeks for degeneration; then removing the pancreas and extracting the residue. He then injected a totally depancreatized dog with this residue and kept the dog alive till the supply of residue ran short and then the dog died. He next conceived the idea that the pancreas of the foetal calf appeared to be a likely source since it contained abundant islet tissue and it seemed probable to him, that, since digestion is not called into play till after the birth of the animal, digestive ferments would not be present in the foetus. His conjecture proved to be correct and experiment proved that extracts from the foetal calf's pancreas lowered the blood-sugar of depancreatized dogs. He also found that this active principle of the gland could be

extracted with acetone and alcohol and was not destroyed by chloroform or ether. In 1922 insulin was first used in the Toronto General Hospital with gratifying success and to-day it is used throughout the world.

In 1924, The League of Nations (26) fixed the definition of the unit of insulin which is as follows:-

"The unit of insulin is one third of the amount of material required to lower the blood-sugar of a two Kilogram rabbit, which has fasted twenty-four hours, from the normal level 0.118 per cent to .045 per cent over a period of five hours". More recently the international unit has been made 40 per cent stronger than this.

Thus, due to patient and persevering medical research work, the physician of to-day is able 3500 years after its earliest recognition, to treat Diabetes Mellitus with confidence and success.

Etiology.

When Mering and Minkowski (14) in the year 1889 produced experimental diabetes by the extirpation of the pancreas, the tendency to ascribe all cases of diabetes to defective pancreatic function was very great. Since then however, post-mortem examinations of some cases of diabetes mellitus have shown neither a macroscopical nor a microscopical change in the pancreas. It must therefore be assumed that the defective factor in these cases is a so-called functional one. Maclean (27) points out that this lack of evidence of pancreatic involvement is so unlike the usual experience in other pathological conditions that it is possible that these cases are not pancreatic in origin but that the primary defect may be in the liver. Joslin (28) and Lawrence (29) are of the opinion that the pancreas is the organ primarily at fault in every case. Joslin states that in those cases in which neither macroscopic nor microscopic change can be demonstrated the method of investigation may be at fault. Allen states that in nearly 100% of cases a hydrops of the beta cells and an absence of Bensley's specific granules can be demonstrated. The most widely held view

to-day is that all cases of diabetes mellitus are caused by a defective function of the pancreas, this defect being either organic or functional. The cause of the defect is not known but many facts attendant upon its establishment are known and will now be discussed.

Obesity.

Joslin (30) states that of all the factors which predispose to the disease that of obesity stands out pre-eminently. From two series of cases, one in 1923 and the other in 1926, he shows that in 2000 cases investigated, 76% were above normal weight. In another investigation he found that in 252 cases of diabetes in patients between the ages of 51 and 60 only two had a subnormal weight prior to the onset of the disease.

Working in conjunction with White, (31) Joslin found that 90% of 100 diabetic children were overweight prior to the onset of the disease. The same investigations showed that, out of a series of 925 adults, 80% were overweight.

From these figures Joslin concludes that diabetes is largely a penalty of obesity and states that

the simple procedure of maintaining normal weight will prevent the onset of the disease. Joslin states that to all his obese patients he preaches the doctrine of under-eating and over-exercising.

Lawrence (32) also states that the most noticeable cause in the production of diabetes, except in acute cases, is over-eating and obesity. He cites an example supporting this of the greatly diminished incidence of diabetes among the underfed Germans during the war. Labbé (33) recognises a pre-diabetic stage in the obese but John (34) is of the opinion that the dysfunction of the pancreas, among other glands, is primarily responsible for the obesity and not the obesity for the pancreatic dysfunction.

Heredity.

Cambridge (35) emphasises the hereditary factor in the occurrence of the disease. He is of the opinion that diabetes mellitus or a condition predisposing to its development tends to run in families and is a hereditary taint. He found that 28% of 800 of his cases gave a family history. He is not clear whether the inherited factor is itself the determining cause or whether this merely predisposes to the disease.

Occurrence in children without demonstrable cause is in favour of an inherited factor and the occurrence of diabetes in association with infections and other recognised causes is in favour of an inherited pre-disposition. Cammidge is of the opinion that the inherited factor or pre-disposing factor has not been proved to be the basis for development of diabetes in all cases but there is sufficient evidence to show that the marriage of diabetics is inadvisable and that intermarriage between families with histories of the disease should be discouraged. In a recent paper Cammidge (36) shows that, out of sixteen cases of diabetic retinitis investigated, ten had a family history of the disease.

Hurst (37) states that 22% of his investigated cases showed the inherited factor, that coincidence could not account for more than half this percentage, and that undoubtedly the disease can be transferred from generation to generation. He points out that as a result of insulin treatment the diabetic incidence is bound to rise as many diabetics who would have died or would have been impotent in pre-insulin days are now capable of fecundity.

Joslin (38) hesitates to attach much importance to heredity. He points out that diabetic patients naturally know more of the presence of diabetics in their own families than non-diabetic patients do. 18% of Joslin's diabetic patients showed a family history of the disease and 7% of his non-diabetic patients had relatives with the disease. Joslin looks on heredity as a favourable factor in the prognosis of both young and adult diabetics.

Infections.

Many authorities are of the opinion that an infection is the etiological factor in the production of diabetes mellitus. Barach (39) constructed a curve indicating the relative frequency of all preceding infections in 1500 cases of diabetes and he found that chronic tonsillitis and typhoid fever were markedly associated with the disease. In the interpretation he points out that the effect of the constant effect of the toxins produced in a chronic tonsillitis on the insulin-producing tissues so damages these tissues that diabetes results and in the case of typhoid fever the toxic effect is so severe that permanent injury of the pancreas results.

Evans (40) shows that oral sepsis causes a marked diminution in carbohydrate tolerance and leads, if prolonged, to the condition of diabetes in many patients. Langley (41) describes two cases of glycosuria, in one of which there was a fistula-in-ano of ten years duration and in the other a large carbuncle. In both cases the glycosuria disappeared when the infective conditions were cleared up.

Lecocq (42) reports the occurrence of diabetes following an infection in seventeen cases of children.

Syphilis has been shown to be a cause. Wodon Duffrane (43) describes a case in a man with syphilis of 34 years duration. Within one month of the institution of anti-syphilitic treatment he states that the hyperglycaemia disappeared. Joslin (44) states that in a few cases only, has he been able to associate infections with the onset of the disease. He points out that a distinction must be drawn between an infection as the etiological factor and the well-known effect of an infection in aggravating an existing diabetic condition. Further he points out that syphilis is a rarity in diabetic patients. Of 3200 of his cases only 1.7% showed signs or gave a history

of syphilis. Lawrence (45) in an interesting article on the effect of toxins on carbohydrate metabolism carried out the following experiment. He injected a rabbit with a dose of diphtheria toxin, the amount of which he calculated was sufficient to kill the animal in from four to eight days. He found in this rabbit that a dose of insulin which had previously caused a considerable fall in the blood-sugar now failed to do so. This phenomenon did not take place on the first day but became noticeable when the action of the toxin was fully established. On the death of the animal marked histological changes were found in the thyroid and adrenal glands. They showed great congestion with disappearance of the colloid and lipid substances. In all infections it is known that the resultant toxins produce a physiological hyperactivity of these glands and it is also known that the secretion of these glands are antagonistic to insulin.

The significance of this experiment is that the toxins of an infection call forth a hypersecretion of the thyroid and adrenal glands and that these secretions antagonise insulin and that a strain is thus

put on the insulin producing mechanism in an endeavour to produce sufficient insulin to neutralise this antagonistic action. This strain will vary indirectly with the degree of the virulence of the toxin or directly with the degree of response called forth from the thyroid and adrenal glands.

Nervous Factor.

The fact that in a number of diabetics there is an antecedent history of mental strain has given rise to the theory that the factor in production of the disease may be nervous in origin.

The glycosuria resulting from puncture of the medulla oblongata between the 8th and 10th cranial nerves, first demonstrated by Claud Bernard, (46) led observers to consider the possibility of there being a "sugar centre" in the brain. Bougach (47) produced a hyperglycaemia by stimulating the vagus centre in the brain. It has since been found that the hyperglycaemia produced in the former experiment was caused by a stimulus to the suprarenals via the cord and splanchnic nerves producing a liberation of adrenaline and in the latter experiment by a direct stimulation of the liver through the vagus nerve

causing glucose to be poured into the blood stream. Cases occur when the presence of a cerebral tumour, a cerebral haemorrhage or meningitis cause the appearance of sugar in the urine. Low, (48) points out that this is due to pressure on the floor of the 4th ventricle. Neilson (49) is of the opinion that the nervous factor is a complex but definite one in the production of the disease. He points out the frequency with which emotional upsets and severe mental strain are associated with the onset of the disease and the frequency with which they aggravate an already established case of diabetes. Joslin (50) states that mental workers follow a sedentary occupation which causes underexercise and usually over-eating. This leads to obesity which, as shown above, he considers the pre-eminent etiological factor. He has however been struck by the fact that children who stand exceptionally high in their classes at school figure largely in the cases which have come under his care, and, because of this, he cautions his professional associates whose children are exceptionally brilliant.

Joslin (51) found that of 40,000 American

troops who passed through his hospital in France, only two were diabetic. All these men had been subject to severe mental strain. It must be noted though that these American troops suffered at the most only four months of mental strain and this during attack. The effect of four years mental strain on the British, French and German troops during both defence and attack on the incidence of diabetes can only be surmised.

Lawrence (52) is of the opinion that anxiety or mental overstrain predispose to diabetes and certainly aggravate it.

Liver.

In an important article Loewi (53) shows by experiment that in diabetes there exists a direct inhibition of the utilization of glucose by the cells of the body and that this inhibition is caused by an excessive secretion of a substance called "glycemin" by the liver. He considers that the liver disorder which causes this excessive "glycemin" secretion is the primary cause of diabetes. Joslin (54) states that this discovery may lead to a revision of all ideas on the etiology of the disease.

Thyroid Gland.

Hyperthyroidism precedes diabetes much more frequently than diabetes precedes hyperthyroidism. The pancreas and thyroid glands have antagonistic actions. The former lowers glycaemia and fixes glycogen in the liver; the latter raises glycaemia and removes glycogen from the liver. Many authorities are of the opinion that exhaustion of the pancreas is produced by its attempt to neutralise the antagonistic hypersecretion of the thyroid which occurs in hyperthyroidism.

Joslin and Lahey (55) treated an equal number of cases of hyperthyroidism associated with diabetes by different methods. Joslin treated his cases by means of diet and insulin thus aiding an underfunctioning pancreas. Lahey treated his cases by the surgical process of removal of part of the thyroid gland, thus lessening the effect of an overfunctioning thyroid. The final results of both lines of treatment were very similar.

The question arises, which is the exciting factor? Does a hypofunction of the pancreas, leading to sugar starvation of the cells of the body, call

forth a physiological response on part of the thyroid gland to hypersecrete thyroxin? Or does a hyperfunction of the thyroid gland lead to a hypofunction of the pancreas produced by exhaustion? Of 4,917 cases of diabetes treated by Joslin, he found that 1.52% had an associated hyperthyroidism. Of 3,869 cases of hyperthyroidism operated on by Lahey, he found that 3.85% had an associated diabetes.

Labbé (56) is of the opinion that they are totally distinct diseases occurring together only in rare cases.

Pituitary Gland.

Martin (57) in discussing the pathology of pituitary tumours with reference to their association with glycosuria found that in 90% of these cases the tumour was benign, consisting typically of eosinophile cells. Malignant tumours, in his experience, do not give rise to diabetic symptoms. He considers that pressure in the region of the 4th ventricle is not sufficient to explain acromegalic diabetes and that the excess of pituitary secretion found in acromegaly produces a disorganisation of the pancreatic, thyroid and ovarian glands leading to glycosuria.

It is known that injections of pituitrin, the internal secretion of the posterior lobe, will produce hyperglycaemia but in acromegaly the essential defect is hypertrophy of the anterior lobe and the prevailing expert opinion appears to be that in acromegaly the hyperglycaemia produced is caused by pressure on the floor of the 4th ventricle, producing as has already been shown, a stimulation of the suprarenals via the cord and splanchnic nerves.

Ovaries.

Carnot (58) describes the case of a woman in whom diabetes was not relieved by diabetic treatment. A glycosuria was constantly and a ketonuria frequently present. He found that insulin abolished the ketonuria but not the glycosuria. Prior to the first symptoms of diabetes menstruation was delayed, then scanty and finally absent. He injected one c.c. of an ovarian extract every second day and with the second injection a rapid fall in the glycosuria ensued. In ten days time the glycosuria disappeared and the menses restarted after three months cessation. He concludes that there is a close relationship between some cases of diabetes and ovarian disturbance and that ovarian

secretion may relieve glycosuria and hyperglycaemia where insulin fails.

Race, Age, Sex.

As regards race, age and sex incidence, diabetes is commoner amongst Jews than Gentiles. It is comparatively rare amongst Italians and Japanese. It occurs at all ages of life and both sexes appear to be equally affected though the incidence in women over 55 is apparently on the increase.

Joslin (59) points out that the disease is only commoner in Jews than Gentiles because as a race the Jews are more obese.

On considering all these etiological factors in the production of diabetes mellitus it appears to the writer that there is a missing link in the production of the disease. One authority shows that obesity occurs in a very high percentage of cases and considers that over-feeding leading to obesity is the primary etiological factor. But all diabetics are ^{primarily} not obese and all obese are not diabetic.

Another authority lays stress on the hereditary factor but in most cases of diabetes no family history can be demonstrated.

A third authority points out the undisputed effect of an infection on the insulin-producing mechanism, but again comparatively few infections even of the most severe type are followed by diabetes.

Other authorities show a close relationship between nervous, liver, thyroid, pituitary and ovarian upsets and diabetes, but again the occurrence of diabetes following upsets of this nature is the exception and certainly not the rule.

The writer suggests that two factors are present in every case of diabetes. The first factor is the presence of an "exciting factor" and the second factor is the probable existence of an ultra-microscopic virus with a specific affinity for the pancreas, called the "specific factor".

The "exciting factor" may be:-

- (1) Obesity produced by over-eating which has caused a constant strain on pancreas. Or
- (2) An infection producing an indirect strain on the insulin-producing mechanism. Or
- (3) An inherently weak pancreas. Or
- (4) A nervous liver, thyroid, pituitary or ovarian lesion producing an upset of the pancreatic secretion.

It is suggested that the "specific factor" (i.e. the specific ultramicroscopic virus) is unable to attack with success a normal pancreas unless the "exciting factor" is present and this exciting factor so devitalises the pancreas that the "specific factor" is able to gain an entry and produce the pathological condition of diabetes mellitus. One or more conditions may be present to produce the "exciting factor". In a child the effect of an infection in the presence of an inherently weak pancreas may so render the pancreas incapable of withstanding the attack of the "specific factor" that diabetes ensues. Sustained strain on the insulin producing mechanism will naturally lower the resistance of the pancreas more than a short strain. Thus overeating as an "exciting factor" will devitalise the pancreas more than an infection as an "exciting factor" and this will explain the high incidence of diabetes amongst the obese.

In hyperthyroidism there is a constant excessive secretion of the thyroid gland leading to a constant effort on the part of the pancreas to maintain the normal endocrine balance in the blood. This constant strain will act as "exciting factor" and will explain

the comparatively high incidence of diabetes in this condition.

The occurrence of the "specific factor" in the body cannot be common; for, in a community where over-eating, infections and the other exciting factors mentioned are so common, the diabetic incidence would be much higher.

In those cases where no changes can be demonstrated histologically in the pancreas, may it not be that the changes present are ultramicroscopic? - and that the method of investigation is inadequate?

By a removal of the "exciting factor" and by dietary measures either with or without insulin, the pancreas is able to regain its lost resisting power and vitality with a consequent subjugation of the "specific factor" though probably in most cases a permanently disabled pancreas is left.

Normal and Abnormal Metabolism.

In diabetes the primary defect is a derangement of the carbohydrate metabolism but, as this derangement leads to an upset of the general metabolic processes of the body, then the abnormal metabolism of the other foodstuffs must be considered. In this section a short description of the normal metabolism of the three main foods and of the abnormal metabolism as found in the diabetic, will be given.

Carbohydrate Metabolism.

Carbohydrate food is absorbed from the upper intestinal tract in the form of monosaccharides, mainly as glucose, and is carried to the liver and muscles where it is stored as the polysaccharide glycogen. After the ingestion of a meal the normal amount of sugar in the blood is temporarily increased. The normal amount of fasting blood-sugar varies between .08% and .12%, - .1% being taken as an average fasting blood-sugar level for normal individuals. This fasting blood-sugar percentage is higher in elderly people, the significance of this being discussed under Diagnosis. After the ingestion of food the blood-sugar percentage rises from the basal figure of

.1% to a maximum concentration which varies between .15% and .18% - .17% being taken as the average blood-sugar maximum of normal individuals. Many authorities take .18% as a maximum blood-sugar figure but .17% is the figure suggested by Joslin. Again this figure is usually higher in elderly people.

The maximum blood-sugar concentration is reached within an hour, usually within forty minutes of taking food and in about the same number of minutes as it took to gain its maximum it falls to a ^{slightly} lower level than it started from. The height of the rise of the blood-sugar curve varies with the amount and type of carbohydrate food ingested. Lawrence (60) shows that after tea the rise is greater than after other meals because more quickly absorbable carbohydrate food is eaten then. Graham (61) shows that the height of rise varies with the general health, the carbohydrate tolerance being greater after a holiday than before it. The rise in the blood-sugar percentage after a meal is due to the amount of sugar absorbed into the blood-stream and the fall is due to the intervention of the sugar storage mechanism, the sugar being abstracted from the blood more quickly than it enters. It is interesting to note that this inter-

vention occurs^{at} about the point at which the kidneys begin to excrete sugar in the urine. This point is called the renal threshold and it varies but on an average when the amount of sugar in the blood exceeds .17% the kidneys excrete the excess. In some individuals the threshold is low producing a type of glycosuria which is termed Renal Glycosuria. This type is discussed under Diagnosis.

When the muscles and tissues require glucose for the production of energy the body stores of sugar are activated to pour out glycogen as glucose into the blood-stream. How this liberation of glucose takes place is not exactly known. Cammidge (62) points out that there is considerable experimental evidence to show that the internal secretions of the suprarenal, thyroid and pituitary (posterior lobe) glands inhibit glycogenesis and promote the conversion of glycogen into glucose. Opposed to this group are the internal secretions of the pancreas and parathyroid glands which promote the deposition of glucose as glycogen in the liver and tissues.

Experimentally it is known that the hypodermic administration of adrenaline and pituitrin and the

oral administration of thyroid gland lead to a hyperglycaemia. Overactivity of the thyroid gland frequently leads to hyperglycaemia and in acromegaly a hyperglycaemia is occasionally associated, though Low points out that in acromegaly in which the anterior lobe is affected, this excess of sugar in the blood is caused by pressure on the floor of the 4th ventricle. It will be remembered that Claud Bernard in his classical experiment produced an experimental glycosuria by puncturing the floor of the fourth ventricle.

Hyperglycaemia is rare in cases of Addison's disease, myxoedema and in Fröhlich's disease, in which there is a gradual destruction of the posterior lobe of the pituitary.

As already outlined the beta cells of the islet tissue of the pancreas secrete a substance called insulin, so named by Schaefer in 1916. The action of this internal secretion is twofold; firstly it supplies a link whereby the muscle and tissue molecules are enabled to utilise the circulating glucose and fat molecules with a resultant production of energy and during this metabolic process the glucose

and fat molecules are oxidised into CO_2 and H_2O ; secondly it promotes the conversion of absorbed glucose into glycogen with a deposition of the latter in the liver and tissues. Joslin (63) states that insulin has the further effect of converting part of the protein and fat into sugar.

In diabetes mellitus the essential defect is lessened pancreatic internal secretion and consequently two pathological processes are initiated. Firstly the tissues and muscles are unable to utilise glucose efficiently, and secondly the liver and tissues are unable to store glycogen sufficiently.

The inability to oxidise the glucose is the more important defect; and, as it is not metabolised in the usual way, the glucose accumulates in the blood and when its amount exceeds .17%, it is thrown out by the kidneys. As the tissues are starved of sugar there is a physiological response on the part of the suprarenal, thyroid and pituitary glands to hypersecrete in an endeavour to stimulate the liver to supply sugar and as a result of this the blood becomes further charged with glucose and the body store of glycogen becomes depleted.

In some cases of diabetes the second function appears mainly to be interfered with. Cammidge (64) designates this defective type of diabetes as the "anopathic" variety as opposed to the "achriatic" variety in which there is both a defective storage and glucose utilisation. Maclean (65) styles this variety of defective storage as "hepatic" glycosuria and he does not consider it to be a true diabetes. He points out that this type occurs essentially in elderly people and its prognosis and treatment are different from those of true diabetes. Joslin, (66) Lawrence, (67) and Murray Lyon (68) do not consider that these types can be thus separated and that the difference is merely one of degree in which one defect predominates. Joslin (69) points out that a mild case of diabetes may become very severe by the occurrence of an infection or by the sudden restriction of carbohydrate food with excessive fat administration.

The writer is of the opinion that this "anopathic" or "hepatic" type of glycosuria cannot be considered as a separate variety. It is more a stage or phase in the disease. This does not necessarily mean that the disease will become more severe, as the con-

ception that a diabetic, if he lived long enough, would pass from the mild to the severe condition has been abandoned. As diabetes mellitus occurs mostly in the elderly it seems likely that this defect in glycogen storage is the primary defect and may persist for years but at any time the glucose utilisation defect may become pronounced and the patient may pass into a severe phase, ketosis possibly supervening. The first blood-sugar change which takes place in the diabetic is the lengthening of the time it takes for the sugar curve to regain its normal; increase in blood-sugar percentage over .17% being the second change. This is an important fact for it points to the storage defect being the primary one in the diabetic and it also helps in ascertaining the degree of the diabetic condition present. This is dealt with further under Diagnosis.

Protein Metabolism.

Protein is absorbed from the small intestine almost entirely as amino-acid bodies and it circulates as such in the blood. A minor part of these amino-acid bodies go to repair the tissue wear and tear in the adult and to build up new tissues in the young.

When the tissues have abstracted the required nitrogenous material, the remaining major part of the amino acid bodies are deaminised in the liver. In this process the nitrogen is removed and converted into urea which is excreted by the kidneys and the nitrogen-free amino acid bodies are now available for either carbohydrate or fat metabolism.

Maclean (70) gives the following diagrammatic representation of the path of protein metabolism:

Path of metabolism for Carbohydrate.

Glucose

58%

Glycogen

Glucose.

Eliminated in the urine in diabetes.

Unknown intermediate products.

CO₂ and H₂O

Path of metabolism for Protein.

Some used for renewal of tissues.

46%

Path of metabolism for Fat.

Oxybutyric Acid.
Diacetic Acid. Acetone
Other bodies.

Eliminated in the urine in diabetes.

CO₂ and H₂O

Protein is therefore mainly an accessory supply of carbohydrate and fat for the body. Woodyat (71) has shown that this endogenous supply of glucose and fatty acid must be taken into consideration when computing a diet for the diabetic. This is further dealt with under Treatment.

Fat Metabolism.

Fats are broken down in the duodenum into fatty acids and glycerine and the fatty acids are absorbed into the thoracic duct as neutral fats. These neutral fats are stored in the body and in the subcutaneous tissues and omentum. Little is known of the metabolism of fat but it is surmised that the neutral fats are reconverted into fatty acids and these long chain fatty acids are broken down, two carbon atoms at a time, until some simple substance, such as pyruvic acid results which is then oxidised to CO_2 and H_2O . In diabetes owing to defective carbohydrate metabolism, the fat is incompletely oxidised and the incompletely oxidised fatty acid products butyric acid, β -oxybutyric acid, diacetic acid and acetone are formed. These bodies are termed ketone bodies.

Joslin (72) and Maclean (73) are of the opinion

that these ketone bodies are formed normally during fat metabolism but that in diabetes, because of lack of insulin, they accumulate as unoxidised fat products. This accumulation produces a condition termed ketosis, and the more advanced the ketosis, the greater is the chance of coma supervening. This question of ketosis is intimately bound up with that of acidosis. It is assumed that the acidity of a solution depends upon the relative preponderance of hydrogen ions over hydroxyl ions and that at absolute neutrality the H ion concentration equals the O H ion concentration.

The acid-base equilibrium of the blood under physiological conditions is always kept constant and the system is a very complex one. The addition of acids or alkalies, except in very large quantities, does not alter the reaction of the blood. The equilibrium is maintained by the presence of "buffer" substances in the blood. Proteins, salts and sodium bicarbonate constitute the alkali reserve and act as buffer between the blood and excess hydrogen ions. A depletion of this alkali reserve is termed acidosis and an increase is termed alkalosis and these terms

refer to the quantity of available alkali present in the blood and do not refer to the hydrogen ion concentration of the blood. This is important to note because a patient may be in an extreme condition of acidosis with a normal hydrogen ion concentration of the blood. Depletion in the alkali reserve precedes a rise in hydrogen ion concentration and consequently this is a valuable test for the indication of treatment. A second factor in the maintenance of the acid-base equilibrium of the blood is the renal one. The kidneys help to maintain this equilibrium by secreting either an acid or alkaline urine. Bence-Jones (74) shows that the alkaline urinary tide following a meal is due to the removal of HCL from the blood during gastric secretion, thus leaving the blood in a more alkaline condition. A third factor is the respiratory one. Any tendency to change of the H ion concentration of the blood acts as a respiratory stimulus with the result that CO_2 is washed out of the blood, the body using this weak volatile acid for adjustment of the blood reaction. Thus in acidosis the breathing is deepened in an endeavour to wash out the CO_2 , whilst in alkalosis the breathing

is lessened in an endeavour to retain the CO_2 .
Dodds (75) shows that after a meal the CO_2 tension rises during gastric secretion and falls during pancreatic secretion. The rise during gastric secretion denotes retention of CO_2 due to the alkalosis of the blood following the pouring out of HCL and the fall corresponds to the excretion of CO_2 in the period of acidosis following alkaline pancreatic secretion.

Normally the CO_2 tension varies from 4% to 6%. According to Poulton (76) a value of 2% CO_2 in the alveolar air indicates the onset of coma within 24 hours, while a value of 3% to 4% suggests the probability of coma supervening in 3 or 4 days. The estimation of alveolar CO_2 therefore gives valuable information as to the degree of acidosis present.

In the diabetic there is an accumulation of ketone bodies in the blood and β -oxybutyric and diacetic acids are substances which ionise and are consequently capable of producing acidosis. There is evidence of acidosis in coma since the CO_2 tension and the alkali reserve are lowered and the question arises as to whether coma is produced by the acidosis entirely or whether there is a specific action of the

ketone bodies. Joslin (77a) points out that coma may persist after the alkali reserve has been returned to normal by the administration of alkalis. It would thus appear that the ketones have a specific action. Graham (77b) states that in ketosis there is usually no change in the H ion concentration of the blood. This question is further dealt with under the discussion of alkali administration in cases of coma.

As the body is unable to oxidise these ketone bodies it endeavours to excrete them by the kidneys as in severe cases of diabetes the urine contains β -oxybutyric acid, diacetic acid and acetone, producing what is termed ketonuria.

Benedict (78) shows that the neutralisation of these abnormal acids probably takes place in the kidneys. Urea is broken down and the free ammonia thus liberated combines with these abnormal acids to form a salt. The kidneys thus conserve the sodium supply of the blood. The presence of large amounts of ammonia salts in the urine indicates the presence of large amounts of acid bodies in the blood and this fact is made the basis of a test for estimating the degree of ketosis present. This is further discussed under coma.

Woodyat (79) shows that during metabolism 100 grams of fat yield 90 grams of fatty acid and 10 grams of glucose. The glucose is derived from the glycerol capsule of the fat molecule. This endogenous supply of glucose must be taken into account when compiling a diet for the diabetic. Woodyat points out that this endogenous glucose supply must still be classified as a theory and is in no sense an established fact. Joslin (80) is of the opinion that much more than 10% of fat is available for glucose supply but he adheres to Woodyat's theory in compiling his diets.

As a result of their study on ketosis Hubbard and Wright (81) confirm Woodyat's theories and come to the following conclusions:-

- (1) That normally there is a balance in the body between the ketogenic substances (fatty acids) and the anti-ketogenic substance (glucose).
- (2) That protein can figure as an anti-ketogenic substance to the extent of 58% of its weight.
- (3) That fat can figure as an anti-ketogenic substance to the extent of 10% of its weight.

Diagnosis.

The differential diagnosis of cases giving a positive Benedict test is very important and the following routine is carried out in all cases. Sugar in the urine is usually first detected by the appearance of one or more of the symptoms of diabetes in the patient which leads the practitioner to perform the test. It may be discovered during a medical examination for life insurance or it may be found in the routine examination of a patient's urine. It has been the aim of the writer to persuade each of his patients to have a yearly "over-haul" the patients birthday being the suggested day on which to have it; for among other conditions, it is felt that a number of early cases of diabetes could be detected in this way.

Apart from the gross signs of the disease of diabetes mellitus (clinical signs of ketosis, severe wasting, gangrene, coma etc.) the following early manifestations of the disease are of great importance to the practitioner and they have been arranged in order of frequency as found by Joslin (82).

(1)	Loss of strength.....	73%	of 200 consecu-
(2)	Polyuria.....	69%	tive cases.
(3)	Excessive thirst.....	62%	" " "
(4)	Excessive hunger.....	55%	" " "
(5)	Pruritus.....	27%	" " "
(6)	Loss of weight.....	21%	" " "
(7)	Pains in extremities.....	17%	" " "

A patient complaining of one or more of these symptoms has a urinary examination performed.

Benedict's qualitative test for sugar in the urine is the one employed in the writer's practice. The procedure of testing is as follows. To one inch (5 c.c) of Benedict's solution, eight drops of the suspected urine are added and the solution is boiled for two minutes in a spirit flame. If there is much sugar in the urine the blue colour will be replaced by a yellow or red colour. If there is little sugar the solution turns green. In this case the test tube is allowed to stand for ten minutes when a red-yellow deposit indicates a positive test. Without this deposit the test is negative although the colour may have changed. The test depends on the formation of

reduced copper oxide.

When a patient has been found to have a positive Benedict test he is considered to have diabetes mellitus till the contrary is proved.

The classification of patients which is used is a slight modification of Joslin's (83) in that potential and early cases are classed together and "lag^{storage}-curve" glycosurics are added. It is as follows:-

- (1) True Diabetics, subdivided into:-
 - (a) Potential or early cases.
 - (b) Medium cases.
 - (c) Severe cases.
- (2) Glycosurics, subdivided into:-
 - (a) Renal glycosurics.
 - (b) "Lag^{storage}-curve" glycosurics.
- (3) Unclassified Diabetics, in which group are placed those cases associated with organic disease (thyroid and pituitary disease, cancer of the pancreas, disease of the liver, etc); those cases of galactosuria and pentosuria and those cases associated with drug-taking, excess of alcohol and emotional strain.

Benedict's test being positive, the first step carried out is the performance of Gerdhardt's and Rothera's tests for ketonuria. Gerdhardt's test consists in adding drop by drop a 10% solution of ferric chloride to one inch of the urine till no further precipitate of ferric phosphate is formed. If a concentration of diacetic acid present is .07%, the solution will turn a port-wine colour. If the patient has been taking aspirin or any other phenyl drug, a positive reaction will also be given. If the urine is boiled, the diacetic acid is converted into acetone and the colour will fade or disappear.

Rothera's test is the more satisfactory ~~test~~ and it consists in taking half a test tube of the urine and adding ammonium sulphate crystals till the urine is saturated. A few drops of a 10% sodium nitroprusside solution are added followed by the addition of a few drops of a 10% ammonia solution. The test tube is well shaken and the production of a permanganate colour indicates the presence of acetone and diacetic acid. There are no fallacies in this test. A positive Gerdhardt test indicates a more severe condition than a positive Rothera test. The importance

of this is dealt with later under Ketosis and Coma.

If these tests are positive then, as Dodds (84) points out, it is fairly safe to conclude that the patient is suffering from Diabetes Mellitus since ketonuria is very rarely present in conjunction with glycosuria except in the diabetic.

These patients are considered as severe cases and are put on a Group "A" diet with insulin at once. This diet is outlined under treatment.

A note may be interpolated here that in pregnancy a lactosuria with an accompanying ketonuria may be present. In pregnant cases therefore a differential diagnosis of the type of sugar present will have to be performed. This will be dealt with further under treatment.

If there is no ketonuria, then a differential diagnosis of the sugar present is performed. Benedict's solution is so constituted that it will not be reduced by such normal constituents of the urine as uric acid, creatinin or glycuronic acid. Dodds (84) states that homogentisic acid occurs so rarely that its presence need not be considered. A positive Benedict's test consequently indicates a glycosuria,

a lactosuria or a pentosuria. A fermentation test is carried out and the method advocated by Maclean (85) is followed. A mixture of the urine and baker's yeast is placed in an Einhorn's tube which is placed near an open fire for two hours. If at the end of that time gas appears at the top of the tube, the presence of glucose is established. If no gas appears then a specimen of the urine is sent to the pathologist to perform the ozazone and Bial's tests for lactose and pentose.

If glycosuria is present then two sugar estimations are performed. A modification of the method advocated by Lawrence (86) is used. A blood specimen is taken before breakfast and a second one is taken one hour after breakfast, the breakfast being the normal average breakfast of the patient. These specimens are sent to the pathologist. If the fasting blood-sugar is above .13%, then diabetes is clearly established. If the figure one hour after breakfast is above .2%, except in the aged (to be discussed later) then again, in the absence of organic disease (hyperthyroidism, hyperpituitarism etc), diabetes is diagnosed.

Sugar tolerance tests are not performed in these cases. Lawrence (87) points out that they are harmful and are quite unnecessary.

If the blood-sugar figures come below the above specified standards, then a sugar tolerance test is performed. Patients are sent to the pathologist for the performance of this test. As the fasting blood-sugar has already been determined four blood-sugar estimations are carried out at half-hourly intervals after the patient has ingested 50 grams of sugar.

Normally, as shown under Metabolism, the average fasting blood-sugar is .1% and the normal blood-sugar curve reaches its maximum (which is always less than .17%) usually in about forty minutes time and in about forty minutes time from its maximum attainment the curve has dropped to slightly below starting point. With the five blood-sugar figures, the differential diagnosis may be completed:

Potential or Mild Case.

If it is found that there is a delay in return of the curve to the normal level but a .17% blood-sugar is not exceeded, then the patient is a potential or mild case of diabetes. These cases, it will be



observed, are very difficult to detect clinically as they are invariably symptomless and the glycosuria is intermittent and only discovered by chance.

Medium Case.

If it is found that the curve rises above .17% and there is a delay in the return to normal blood level, then the patient is considered to be a medium case of diabetes in the absence of ketonuria.

Severe Case.

If it is found that in conjunction with a raised blood-sugar percentage there is severe wasting, the patient is considered to be a severe case. Cases showing ketonuria have already been discussed.

Renal Glycosuria.

If the curve is a normal one, then the case is one of Renal Glycosuria. As pointed out under Metabolism the renal threshold is lower than normal in these cases and the kidneys "leak" sugar. Glycosuria may be present only after meals or, if the threshold is very low, it may be constantly present. Most authorities are of the opinion that this type of glycosuria is harmless.

Lawrence (88) shows that it is possible for a

true diabetic to have a low renal threshold. This is only detected when the blood-sugar is shown to be below the normal level with glycosuria persisting. He is of the opinion that there is no reason to think that the combination of diabetes mellitus with a lowered renal threshold is not a mere coincidence. Maclean (89) points out that it is not uncommon for elderly diabetics to have a raised threshold. It is invariably associated with kidney changes and these cases are only diagnosed as suspects. The prognosis, he points out, is bad.

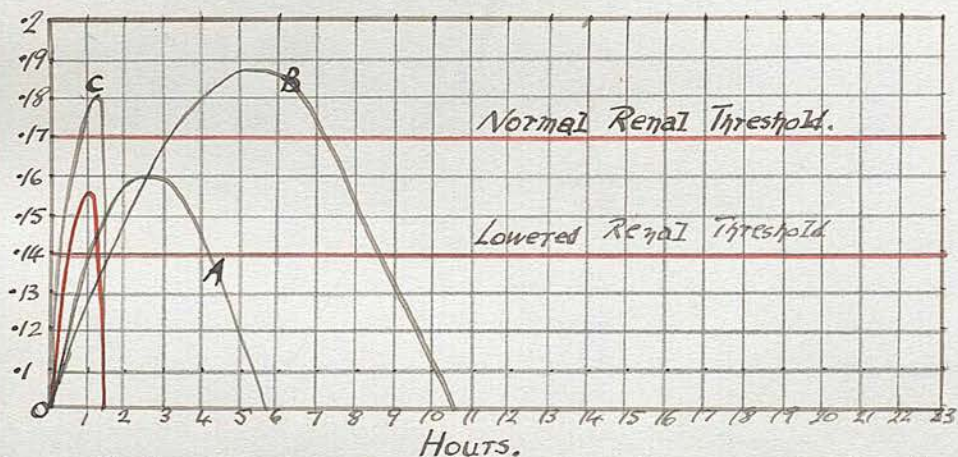
"Lag^{storage}-curve" Glycosuria.

If the curve exceeds .17% but falls suddenly and is normal or slightly below normal within one and a half hours time, then the case is one of "Lag^{storage}-curve" Glycosuria. This is a rare type of glycosuria described by Maclean (90) and his explanation of its occurrence is that the mechanism for keeping the blood-sugar level below the threshold is later than normal in exerting itself. There is no deficiency in the storage mechanism.

Graham (91) advises the repetition of the sugar tolerance test in these cases of "lag^{storage}-curve" glyco-

suria in three months time. He considers them potential cases of diabetes.

The blood sugar curves which may result from the sugar tolerance test may be represented thus diagrammatically:



Red curve represents a normal or a renal glycosuria curve.

A. Curve represents a potential or early case of diabetes.

B. Curve represents a medium case of diabetes, *in the absence of ketonuria, severe wasting, etc.*

C. Curve represents a "lag^{storage}-curve" glycosuria.

The ability of the patient to regain a normal blood-sugar level within a limited time after the ingestion of 50 grams of sugar is the best indication of an effective carbohydrate system.

Alimentary Glycosuria.

Alimentary Glycosuria is essentially of the same nature as the glycosuria of diabetes as in both cases there is a defective carbohydrate mechanism. The classical view was that if an excessive amount of sugar is taken, the liver becomes saturated with glycogen and the excess sugar passes into the blood stream producing hyperglycaemia. Taylor and Hulton (92) showed that in a normal individual it is impossible to produce glycosuria by forced glucose ingestion. Bennett and Dodds (93) found that 500 grams of glucose did not produce glycosuria in a normal man and Maclean (94) points out that the normal storing mechanism should be sufficiently active to prevent any amount of ingested sugar from raising the blood-sugar percentage. Lawrence (95) is also of the opinion that glycosuria appearing after the ingestion of any quantity of sugar denotes a defect in carbohydrate metabolism. Most authorities are of the opinion that the term alimentary glycosuria might be dropped with advantage.

Before making a final interpretation of the sugar tolerance test curve the following facts must be taken

into consideration.

Foster and Langley (96), in an important article, show that:-

- (1) The fasting blood-sugar level varies normally from .08% in children to .15% in those over 70 years of age.
- (2) The actual increase in blood-sugar percentage after ingestion of food remains the same and is always less than .1%.
- (3) The time of the maximum blood-sugar concentration is lengthened with age, i.e. in the elderly the maximum is liable to be one hour after food ingestion as compared with half an hour in youth.
- (4) There is a delay in return to normal blood-sugar level with advancing age.

Unclassified Diabetics.

Unclassified Diabetics include the remaining cases of glycosuria. It is not within the scope of this thesis to outline the differential diagnosis of these cases. Glycosuria is most frequently found in association with lesions of the thyroid and pituitary glands. It may be met with in organic disease of the

liver, kidneys or pancreas. It may be associated with trauma or an infective process in the region of the pancreas. A glycosuria may be found after the administration of an anaesthetic or after alcoholic excess. Folin (97) showed that 18% of students who had just undergone an examination showed a glycosuria thus demonstrating the effect of emotional strain. This is probably due to an excess liberation of adrenaline.

As has been shown, sugar in the form of lactose or pentose may be found in the urine. Lactosuria occurs in pregnant and lactating women and is considered a harmless condition. Pentosuria is an inborn error of metabolism and, so far as is known, has no deleterious effect on the patient's health. It occurs mostly in those of the Jewish race.

The author has met with two cases of lactosuria in practice, Mrs.P. in November 1925 and Mrs.G in June 1928. The condition was detected during antenatal examination. Both patients maintained good health during pregnancy and the confinements were normal. It was noticed in both cases that the breasts were full and "ropey". The lactosuria disappeared four weeks and six weeks respectively after parturition.

Prognosis.

Joslin (98) states that the prognosis of the diabetic depends on four factors.

- (1) The general condition of the patient, apart from the existence of diabetes.
- (2) The patients disposition and intelligence.
- (3) The severity of the disease.
- (4) The zeal of the doctor in attendance.

He is of the opinion that the mild character of most cases cannot be too strongly emphasised. Cases appearing severe at first are often so because of some temporary infection or by the sudden intervention of a fat-protein diet.

Lawrence (99) states that in diabetes more than in any other disease, the prognosis depends on the correct treatment. The complications of diabetes are important and the diabetic usually dies of a complication rather than of his disease. Arterio-sclerosis is the pre-eminent complication and its presence or absence controls the prognosis. Infections, pregnancy and coma increase the gravity of the disease. Joslin (100) states that carelessness ends the life of many a diabetic and consequently in careless

patients he cuts the expectancy of life in half.

Joslin is unwilling to say that treatment effects a cure. His dictum is "Once a diabetic, always a diabetic". Dietetic treatment with or without insulin, however does prolong life and this can best be shown by quoting Joslin's (101) statistics. In 1924 he was able to state that diabetics who formerly died at the age of 41 were now living to the age of 52, and in 1927 he was able to show that the average age at death was 60.9 years.

Allen (102) states that a return to normal blood-sugar may take place in the following cases:-

- (1) Diabetes resulting from a trauma or a local infection in the region of the pancreas, when the local condition has subsided.
- (2) Diabetes associated with organic disease: Hyperglycaemia associated with nervous diseases, cancer of the pancreas, cirrhosis of the liver and tuberculosis may completely disappear. It is thought that the cachexia associated with these organic diseases is responsible for the disappearance of the hyperglycaemia.
- (3) He points out that a considerable number of cases of diabetes of a temporary nature in

children are beginning to appear in medical literature.

Maclean (103) states that insulin will not cure diabetes in severe and long-standing cases. In the young he has found that many of his cases require much less insulin than they did to begin with and he attributes this to a regeneration of the islet cells of the pancreas. In no single case, however, was he able to discard insulin altogether.

Murray Lyon (104) is of the opinion that diabetes is not necessarily a continuously progressive disease and that insulin therapy probably promotes complete arrest in many cases.

Harrison (105) states that no case of diabetes should be pronounced cured.

Concerning the prognosis of diabetes in children there appears to be a diversity of opinion. All authorities are agreed that diabetes occurring in children is apt to be of the severe type and the diabetic child invariably requires insulin. Lawrence (106) points out that because of the severity of the disease and because of the difficulty of control the prognosis must necessarily be less favourable than in the adult

but Joslin (107) states that the younger the diabetic then the greater is the expectancy of life. He points out that most so-called cures have occurred in children. Joslin also considers the presence of a hereditary taint as a favourable omen in children.

The writer is of the opinion that a guarded prognosis should be given in every case. The prognosis depends on the correct treatment both on the doctor's and the patient's parts, and on the presence or absence of arterio-sclerosis.

It is thought that the term "arrested" instead of "cured" might be applied with advantage to those cases becoming sugar free under dietetic treatment with or without insulin.

Treatment.

Having completed the differential diagnosis, the practitioner is next confronted with the treatment of the diabetic patient.

On this subject of treatment there appear to be two schools of thought. One school selects a generous diet, based on the assumption that a man requires 3,000 calories and a woman 2,500 calories a day; and then proceeds to administer insulin in sufficient doses to control the diet and keep the urine sugar-free. The second school assumes that the optimum diet for the diabetic is the lowest one which will sustain the patient's strength, at the same time keeping the blood and urine content within normal limits to which end insulin may or may not have to be administered; and if administered then the insulin dosage is the minimum one to achieve the purpose.

To the former school belongs Falta, (108) and he believes that a diabetic should be dieted like normal individual, his diet being controlled by insulin. He does not permit of any procedure which threatens the patient's nutrition. He instructs his patient as to how to test his urine and to increase the insulin

when sugar appears. He considers it important to make the patient his own doctor. In short he believes that restricted diets are inefficient and that removal of sugar by dietetic means is bought too often at an excessive price.

Widmas and Wagner (109) support this view and they emphasise the value of a high caloric diet and the negligible influence of fats on the blood-sugar, especially in children. They point out that a pancreas will not regenerate on a restricted diet.

Chabanier and Copeman (110) consider that every case of diabetes mellitus presents an indication for treatment with insulin. They consider that mild diabetics, known clinically as "gras", should be treated with insulin even when the glycosuria can be controlled by dietetic means alone. They found it easier to persuade their patients to continue treatment over long periods when the minimum of dietetic restrictions was imposed.

This school emphasises the fact that too much attention is paid to the disease rather than to the patient. It considers that the psychological effect of constant attention to a restricted diet is too

little regarded and often totally neglected.

To the latter school belong Joslin (111) Allen, (112) Lawrence, (113) Maclean, (114) Rabinowitch, (115) Murray Lyon (116) and Harrison, (117). Reference to these experts shows that they are of the unanimous opinion that the optimum diet for the diabetic should not only be low in carbohydrate content but also in total caloric value, whether insulin is or is not administered. Allen's important experiments on dogs, already referred to in the Historical Survey, proved conclusively that the correct treatment was to give the minimum diet necessary for existence as excess diets produced progressive degeneration of the essential pancreatic tissue. Even with the advent of insulin this school believes that the careful regulation of the food intake still remains the most important factor in the treatment of diabetics.

The writer adheres to the second school of thought and this "minimum" diet is made the basis of all diets employed in the treatment of diabetics met with in practice.

In computing a diet for the diabetic, the method devised by Murray Lyon (118) is followed. In the

diabetic the diet, particularly the carbohydrate content, has to be restricted to allow of its balance by the patient's exogenous insulin if possible. For clinical purposes it is sufficiently accurate to assume that:-

1 gram of carbohydrate	=	4 calories.
1 gram of protein	=	4 calories.
1 gram of fat	=	9 calories.

Since fat is therefore a more valuable food than either carbohydrate or protein, it is desirable that the patient's diet should contain as much fat as possible. But there is a limit to which fat can be given. As shown under metabolism, fat is oxidised in the presence of sugar and Woodyat (119) has shown that a ratio of carbohydrate content to fat content of 1: 1.5 must be preserved if this oxidisation is to take place. In other words for every $1\frac{1}{2}$ grams of fat in the diet an equivalent gram of carbohydrate must be present. In compiling a diet to meet this requirement the endogenous as well as the exogenous supply of fat and carbohydrate must be taken into account. Woodyat has shown that:-

100 grams of carbohydrate during metabolism yield

100 grams of glucose and no grams of fatty acid;
100 grams of protein during metabolism yield 58 grams
of glucose and 46 grams of fatty acid and
100 grams of fat during metabolism yield 10 grams
of glucose and 90 grams of fatty acid.

If C is taken to represent the carbohydrate,
P the protein, F the fat, G the glucose and
FA the fatty acid, then the total amount of
glucose available for metabolism may be expressed by
the formula:-

$$G = C + .58P + .1F;$$

and the total amount of fatty acid available for
metabolism may be expressed by the formula;

$$FA = .46P + .9F.$$

Now the correct proportion of FA: G is founded on the
assumption that one molecule of glucose with a mole-
cular weight of 180 will completely oxidise one mole-
cule of fatty acid with a molecular weight of 260.

Thus: $\frac{FA}{G} = \frac{260}{180} = 1.5$

Substituting the FA and G in the previous equations

$$\frac{.46P + .9F}{C + .58P + .1F} = 1.5$$

Simplify this $F = 2C + .54P$ or simply $F = 2c + \frac{1}{2}P$.

This formula constitutes the basis for the computation of the diets employed in the treatment of the diabetic. Murray Lyon (120) points out that the unrestricted use of protein in diabetic diets tends to hasten metabolism and is therefore to be avoided. A maximum of 1 gram of protein per kilogram (2.2 pounds) of body weight is allowed per day accordingly in the adult. In the child a maximum of 1.5 grams per kilogram is allowed as children require a relatively higher protein allowance.

The daily number of calories required by the patient varies with his age and height. An average individual requires a minimum of from 25 to 30 calories per kilogram of body weight per day to maintain normal health and activity. Most healthy people consume far more calories than this amount but it is deemed that from 25 to 30 calories per kilogram of body weight is sufficient for the diabetic needs, and indeed for that matter for the needs of all, and the total number of calories is gauged accordingly. The tables devised by Joslin (121) are those which are employed to ascertain the patient's caloric requirements. These tables are found at the end of Joslin's

manual on Diabetes Mellitus and in them the weight the patient should be for his age and height is the one which is taken to calculate the number of calories required.

Murray Lyon's diets are divided into four groups which are constructed for different purposes.

Group "A" Diets.

Group "A" Diets are used with insulin for those types of patient, to be detailed later, who require insulin control. The G: FA ratio is about 2:1 and this excess of glucose is given to complete the oxidation of the fat.

Group "B"Diets.

Group "B" Diets are intended to "desugarise" the patient. The G: FA: :1:1 and this is necessary to maintain the basal metabolism as the diets in this group are below the amount required to do so and the body stores of protein and fat are called upon to make up the deficiency.

Group "C" Diets.

Group "C" Diets are "ladder" diets which are intended to test the limit of the patients carbohydrate tolerance. The G:FA ratio approaches 1:1.5. When

the patient's tolerance is reached and, if it permits of a normal mode of living, then the patient is kept at that level indefinitely or at least for several months. If the patient's limit of tolerance is too restricted to permit of a normal activity, then insulin is used and the diet increased. This forms one of the indications for the administration of insulin to be detailed later.

Group "D" Diets.

Group "D" Diets are constructed for those patients whose tolerance has been tested in the previous group but who require or desire more protein. These are termed maintenance diets.

When the patient has been for some time on Group "D" diet, he is allowed to choose his articles of diet from the "Line" Ration Scheme devised by Lawrence (122). In this scheme each line consists of two halves, the first half containing the carbohydrate and the second half containing the fat and protein and the total value of the line represents 190 calories. The patient is told how many lines he may have per day and he may combine any first half line with any second half line. This "Line" Ration Scheme

has proved to be of great value in practice. It is extremely difficult to influence some diabetics to maintain the necessary rigid diet especially after a lapse of time from the commencement of treatment and this scheme allows of a great variety of foodstuffs and helps to maintain the patient's interest in his treatment.

At a later stage Harrison's (123) "Five-gram" Scheme may be substituted. This scheme will not be elaborated here but it has been found to be of service to the "trained" diabetic.

Apart from those patients who require insulin treatment (to be detailed later), all diabetic patients are put on a B.15 diet which is called the "Test Diet". On this diet mild cases usually become sugar-free in three or four days. If they do not, they are transferred to a B.12 diet. Lower diets than this are only given to ambulant cases who are in a good physical condition. If the physical condition is not good then the patient is confined to bed and the diet is reduced down the B scale till the urine is rendered sugar-free. When this stage is reached the patient is transferred to Group "C". In this group the advance

in diet is made every second day. If sugar reappears, then the patient drops for one day to a diet of half the value. He is again advanced slowly till his tolerance is reached. If his limit of tolerance is too low to permit of normal health and activity, then insulin is administered. If otherwise he is kept at this stage for some months and then, if he wishes a more unrestricted choice of foodstuffs, he is transferred to Group "D" or to the "Line" Ration or "Five-gram" schemes. During the process of "desugarisation", samples of the 24 hours urine are tested daily for sugar. When the urine has been rendered sugar-free a blood-sugar estimation is performed. In some elderly diabetics the renal threshold is raised and there may be a hyperglycaemia with no glycosuria. In these cases the diet at which the urine became sugar-free is persisted with till the hyperglycaemia subsides.

When the patient's tolerance has been established he is taught to examine a specimen of the 24 hours urine daily for sugar and diacetic acid. He is instructed to have a weekly low-day on which half rations are consumed. As much tea, coffee and bovril as the

patient may wish are allowed on these days. Accurate weighing and measuring of the foods are very essential factors in the treatment and their importance is impressed on the patient. Patients are weighed monthly and they are not permitted to exceed normal weight. If they are losing weight, the diet is increased and insulin may have to be employed. If they are gaining weight the diet is decreased. Lawrence (124) points out that the optimum weight for the diabetic and indeed for every one is 10% below the average weight. He shows that this has been proved by Life Insurance statistics.

The removal of septic foci is of great importance in the treatment of the diabetic. When the diagnosis has been established the teeth should be x-rayed, the tonsils and sinuses investigated, the lungs examined for signs of tuberculosis and the abdomen examined with a view to detecting appendix or gall-bladder infection. It has been shown that sepsis is often associated with hyperglycaemia and may be the factor in its production. With the intelligent co-operation of the patient success will attend the persistence of rigid dieting alone but in many cases insulin will

have to be administered in conjunction with the dieting and the indications for the administering of insulin along with these diets will now be considered.

Insulin Treatment.

The rule in deciding which patients require the administration of insulin in addition to the dietary treatment is the one laid down by Murray Lyon (125).

Four types of patients will require insulin:

- (1) Those who present symptoms and signs of ketosis.
- (2) Those who are severely emaciated.
- (3) Those whose limit of tolerance is too low to allow of normal health and activity.
- (4) Those who fail to respond to simple dietary restrictions.

If the patient belongs to type one of this classification he is put on a Group "A" diet.

At this point the early symptoms of ketosis, which are of great importance to the practitioner, will be discussed. The early symptoms are mainly digestive. They are nausea, lack of appetite, colic and abdominal pain. Both insulin and non-insulin patients are warned of these symptoms and are instructed to advise the doctor when any of them occur.

Later symptoms are giddiness, breathlessness apart from exertion (Kussmaul's dyspnoea) and unnatural drowsiness. These symptoms precede coma, the treatment of which is dealt with later.

If the patient belongs to types two or four of the above classification he is put on a Group "B" diet of a sufficient caloric need and insulin is administered to control the glycosuria.

If the patient belongs to type three, then he is kept in Group "C" on a diet sufficient to maintain normal activity controlled by insulin.

In all cases the patient is put on a fixed diet which is calculated to be sufficient in all respects and insulin is administered in increasing doses till the urine becomes sugar-free. The initial dose of insulin will vary with the severity of the disease. In severe cases it has been the practice to start with 10 units of insulin injected twice daily. Otherwise the initial dose is 5 units twice daily. The table of doses suggested by Maclean (126) is the one employed. In this table the insulin is increased by from 2 to 3 units every second day, the increase being first made in the morning dose. As long as

glycosuria persists the dosage is increased. When the glycosuria disappears then the diet and insulin are maintained at this level for three days. The insulin is then increased very slowly, and by very small additions till slight symptoms of hypoglycaemia appear. The blood-sugar at this point is below .1%. The insulin is then slightly decreased and this is taken as the patients level.

Another advantage of this method of Maclean's is that the patient is familiarised with the slight and early symptoms of hypoglycaemia and the ease with which they can be abolished by the appropriate treatment.

Some authorities tolerate and even encourage the maintenance of a slight glycosuria. Joslin (127) declares emphatically against this procedure. He states that there is strong evidence to show that hyperglycaemia leads to the complications of arterio-sclerosis and cataract. This question is discussed further under Gangrene. Added to this is the fact that the patient's morale is sapped if even a slight glycosuria is permitted and in the case of children removal of the necessity to keep the urine constantly sugar-free leads invariably to a complete loss of control of the case.

Time of insulin administration.

The time of insulin administration in relation to the meals varies. As insulin reaches its peak of action in about one hour's time, then it has been the rule to administer insulin half an hour before meals, as sugar tends to reach its maximum concentration in the blood half an hour after the ingestion of a meal. When the blood-sugar is very high then the insulin is administered one hour before the meal. Two injections are given per day before the two main carbohydrate meals. Fletcher and Campbell (128) call attention to the development of ketosis in the later hours of the day if insulin is given in one morning dose only.

At first the patient is under the close supervision of the doctor and during this time all the procedures carried out and their reasons are explained to him so that when the patient's insulin dosage and diet have been established, he has been initiated into the method of treatment. The following instructions are given to him, a short summary of each rule being written down:-

- (1) He is warned of the symptoms and signs of hypoglycaemia, to be detailed later, and the effect of exercise on the insulin, to be detailed later, is explained

to him. He is instructed to carry a small tin box containing twelve lumps of sugar with him at all times. This question is dealt with fully under Insulin Complications.

(2) He is taught to examine his urine daily for sugar and ketone bodies. Lawrence (129) points out that a 24 hour sample gives less information than samples collected at definite periods. He advises tests to be performed on the first urine passed in the morning, i.e. before insulin administration and the urine passed between 12 noon and 1 p.m. Presence of sugar in the second sample means that the insulin is not reducing the blood-sugar sufficiently and that the diet must be decreased or the insulin increased. In severe cases of diabetes there may be a trace of sugar in the first sample as this is the highest blood-sugar point in the 24 hours. It may be very difficult and even impossible to keep this first sample sugar-free with two injections. In all mild and moderate cases the urine should be kept sugar-free and a 24 hours specimen is tested in these cases. Gerhardt's test for ketone bodies is taught. If it is positive or if any of the symptoms of ketosis described above occur, the patient is instructed to

consult his doctor at once.

(3) He is taught to inject his own insulin with aseptic precautions. He is instructed to inject the insulin into his right thigh, left thigh, right leg and left leg alternatively which is a modification of the distribution advised by Joslin (130). Joslin advises arm injection in addition but it has been found in practice that arm injections cause more pain on account of the comparative lack of subcutaneous tissue in the arms and added to this is the fact that patients find difficulty in injecting the right arm with the left hand. He is taught to inject the insulin deeply into the subcutaneous tissue, superficial to the deep fascia to avoid the possibility of local skin reactions which are described under Insulin Complications at a later stage.

(4) He is instructed that should any abnormal symptoms or signs arise he should communicate with his doctor at once.

(5) The rules of general health (avoidance of constipation and of the risk of infections, etc.) are impressed on him as diabetes is greatly influenced by the patient's general condition.

The effect of exercise is explained to him. This is discussed later under Hypoglycaemia. The effect of infections on exogenous insulin has already been described under Etiology. The effect on endogenous insulin is similar and the importance of avoidance of all infections is emphasised to the patient. Rules of weighing already outlined for the non-insulin diabetic, are of course, also applicable to the insulin diabetic.

A blood-sugar estimation is carried out once a month in the early stages of the after-treatment and later at two monthly intervals. Beaumont and Dodds (131) point out that in some chronic cases of diabetes the renal threshold is above normal during treatment with the result that there is a glycosuria although the blood sugar is within normal limits. Hypoglycaemia may thus be inadvertently produced in these cases.

Other minor points may be summarised as follows:-

- (1) The insulin should be stored in a cool dark place.
- (2) The insulin should only be used if it is clear.
- (3) Two needles should be used, one for piercing the rubber cap and filling the syringe and the other for injecting. The rubber cap blunts the needle readily.

(4) The needles should be resharpened frequently.

Treatment of Children.

It is recognised that diabetes in a child is a most serious condition and that, in the absence of insulin, it is liable to prove fatal in a short time. Joslin (132) shows that comparing the Nauyn, Allen and Banting periods the mortality rate in children for diabetes in the first period (1898 - 1914) was 98.4%, in the second period (1914-1922) was 69.2% and in the third period (1922-1926) was 10.9%.

Surely no greater tribute can be paid to the success of insulin treatment than these figures provide.

Maclean (133) reports that of 30 children treated since 1923, all are alive and in good health. Many of the children when first seen were in coma and a few of them developed coma on subsequent occasions.

Most authorities are agreed that insulin must be employed in all cases of juvenile diabetes. The general principles of treatment are the same as for adults but a few special difficulties arise. Children require a relatively higher caloric diet than adults and the difficulty is to give an adequate diet without having to give insulin in too great amounts and too often.

Levy (134) points out that children have a poor toleration for fat and consequently are apt to develop ketosis. He suggests the advisability of allowing a moderate degree of glycosuria to avoid this but Bennett (135) disagrees with this and states that the only hope of cure lies in keeping the urine sugar-free and with this Joslin, as already stated, agrees.

Joslin (136) states that insulin may have to be given four times a day but Lawrence (137) and Harrison (138) advise against this, partly because of the hardening effect on the skin, and partly because of the alarm caused to the child. Lawrence emphasises the importance of frequent urine tests and blood-sugar estimations. As treatment progresses the diet must be raised if the child is not growing or gaining weight, or lowered if weight is excessive the insulin dosage being adjusted accordingly.

Exercise will have to be vigorously supervised by the parents and this is naturally a great difficulty. In children the effects of intercurrent illnesses are apt to be very sudden and serious.

The writer has treated one child in practice. She is aged 8 and has weathered influenza and measles successfully. She receives insulin twice daily and is in a fairly good state of health. She has given more anxiety than any of the other diabetic patients, especially as she is an only child.

Insulin Complications.

During insulin treatment several complications directly attributable to insulin injection may occur.

These complications are:-

- (1) Hypoglycaemia.
- (2) Haematuria.
- (3) Eosinophilia.
- (4) Local skin reactions.

Hypoglycaemia.

Hypoglycaemia is a condition in which the sugar content of the blood sinks to a subnormal value. This subnormal value varies but on an average when the blood-sugar is .08% or under then signs and symptoms of hypoglycaemia supervene.

Maclean (139) shows that in diabetics who have had a high blood-sugar for some time hypoglycaemia reactions occur at a higher blood level than the average .08%, and Harrison (140) shows that the level at which these reactions occur is much lower in children than in adults.

Hypoglycaemia is caused by an overdose of insulin which may be produced either by neglect to take the prescribed meal after an injection or by unwonted

exercise.

Frank (141) states that in unexplained cases the insulin may have been injected intravenously in error. He shows that when insulin is injected intravenously there is a more rapid and intensive fall in the blood-sugar. Lawrence (142) carried out some very interesting and instructive exercise experiments on diabetics under insulin control. From these experiments he showed that:-

- (1) The immediate effect of exercise in increasing the fall in blood-sugar is very great and that this occurs only during the maximum period of insulin-activity; i.e. from one to four hours after the injection.
- (2) The dose of insulin succeeding exercise has often an unusually powerful effect in reducing the blood-sugar, and
- (3) The increase of exercise over days and weeks allows of a reduction in the insulin dosage. In this connection he points out that it is more physiological to increase the diet rather than to reduce the insulin though at a later date an insulin reduction may be possible along with the increased diet.

These effects of exercise are very important from a practical point of view. In 1925 the writer observed that, in the case of Mr. C., on those mornings in which he had a game of golf his morning insulin dosage could be reduced by 5 units. This fact was discovered because during his game of golf slight hypoglycaemic symptoms invariably occurred and the insulin reduction was accordingly made.

Short bouts of exercise do not materially affect the action of insulin. It is only long continued exercise which has the effect of metabolising sugar that has any practical effect.

Harrop (143) has pointed out that absence of food coupled with severe exercise or vomiting leads normally to hypoglycaemia. This is produced by the exogenous insulin of the body acting on a depleted carbohydrate content.

From the description of the symptoms and signs of hypoglycaemia found in current medical literature cases have been divided by the writer into slight and severe cases for purposes of treatment.

(a) Slight Cases. The symptoms and signs of these cases may be summarised as follows:-

(1) Faintness or giddiness.

- (2) Flushing of the face.
- (3) Slight weakness of the limbs.
- (4) Sweating.
- (5) Coldness of the extremities.

Lawrence (144) points out that these early symptoms of hypoglycaemia are probably produced by adrenaline an excess of which appears in the blood as a physiological response on the part of the suprarenals to restore the normal blood-sugar level.

The treatment of these cases is simply the ingestion of several lumps of sugar. The amount of sugar taken is proportional to the degree of the symptoms present. As already pointed out these symptoms and signs are imparted to every insulin-diabetic and the necessary treatment described.

(b). Severe Cases. The symptoms and signs of severe cases may be summarised as follows:-

- (1) Muscular twitchings.
- (2) Diplopia.
- (3) Convulsions.
- (4) Coma.

These cases demand immediate attention. The diagnosis of this hypoglycaemic coma is described under the differential diagnosis of diabetic coma. A note may be interpolated here that angina pectoris developing as the result of hypoglycaemia is likely to be severe and often proves fatal (Maclean). 1 c.c. of a 1/1000 solution of adrenaline should be injected immediately followed by the administration of 20 to 30 grams of sugar by the mouth or if necessary by means of a stomach tube. This is followed up by the injection of 1 c.c. of pituitrin. *Intravenous injection of sugar is described later.*

The adrenaline stimulates the glycogen storage mechanism to pour all available glucose into the blood-stream. Geiling and Briton (145) have shown that pituitrin injected acts directly on the liver cells producing a liberation of glucose. The patient should remain quiet as this aids recovery. Hypoglycaemic symptoms coming on within two hours of the insulin injection are apt to be of the severe type.

The chief danger of hypoglycaemia is its occurrence during sleep.

Haematuria.

Lawrence (146) records two cases of haematuria following insulin injection. Blood did not appear in the urine till some hours after the injection.

Henderson (147) records two cases. Gudeman (148) records one case in which insulin had to be abandoned as haematuria followed every injection.

Lawrence (149), in an analysis of these cases, shows that there is no common factor in production. In both of his cases there was an accompanying ketosis and he is of the opinion that the ketones irritated the kidneys producing the haematuria. All cases so far recorded have occurred in males.

Eosinophilia.

Lawrence (150) has established the presence of eosinophilia in a large proportion of insulin-treated cases and its absence in non-insulin cases. No definite explanation is offered. He offers three possible causes. (1) By virtue of its physiological action, insulin might produce an eosinophilia. (2) It might be an allergic phenomenon produced in susceptible patients or (3) it might be produced by the constant skin irritation of the injections. He is proceeding

with his investigations.

Local Skin Reactions.

Cases in which areas of local fat necrosis resulting from the continued injection of insulin into one small area have been reported in literature. Carmichael and Graham (151) report two cases and they attribute the cause to the presence of a minute amount of fat-splitting ferment in the insulin. Avery (152) in the examination of 21 cases points out that the reaction is a non-specific one, not due to the presence of any ferment in the insulin but due to repeated small traumata to the panniculus adiposus. Lawrence (153) in a paper on this subject points out that all injections should be properly distributed and should be injected deeply into the subcutaneous tissue just superficial to the deep fascia.

Complications of Diabetes Mellitus
and their treatment.

(1) Coma.

The treatment of diabetic coma must be immediate and vigorous. Beaumont and Dodds (154) state that experience has shown that the longer the patient remains in coma untreated the more difficult it is to revive him. First of all a differential diagnosis must be made as quickly as is possible. The cause of coma is usually due to one of three conditions.

- (a) Diabetic ketosis.
- (b) Hypoglycaemia, or
- (c) Uraemia.

There are other conditions, such as cerebral haemorrhage, tubercular meningitis, alcoholism and morphism, which will cause coma but they are eliminated by the history and clinical appearance of the patient.

A short history of the patient should be obtained. If the patient is a known diabetic and his breath smells of acetone, then diabetic coma is suspected. If the patient is taking insulin and has either been taking unwonted exercise or has failed to take a meal following his insulin injection, hypo-

glycaemia is suspected. If the patient is a "kidney" subject and the presence of diabetes is unknown, then uraemic coma is suspected. The onset of the condition is important. If it has been gradual, accompanied by nausea and vomiting, then diabetic or uraemic coma is suspected. Hypoglycaemic coma comes on suddenly.

While this information is being elicited a catheter specimen of the urine is obtained. Two tests are performed; Gerhardt's ferric chloride test for diacetic acid and Benedict's test for glucose.

Gerhardt's test is performed, for if positive it indicates a more severe condition than ^{does} a positive Rothera's test ~~does~~. The explanation of this is that small amounts of diacetic acid will give no reaction with Gerhardt's test but large amounts will.

(A positive Rothera's test indicates the presence of diacetic acid and acetone. In the pre-comatose patient these tests may be used as a kind of quantitative method for ascertaining the degree of the ketosis, a positive Gerhardt's test indicating a more severe condition).

The findings may be tabulated thus:-

Coma of Diabetic Ketosis.	Coma of Hypoglycaemia.	Coma of Uraemia.
Sugar + Diacetic Acid ++	Sugar - Diacetic Acid -	Sugar - Diacetic Acid -

It should be noted that the sugar test in hypoglycaemic coma may be positive as the urine may have been lying in the bladder prior to the insulin injection. The history of the case helps here and if hypoglycaemia is suspected, a second specimen should be obtained and tested.

It is highly desirable that a blood-sugar estimation should be performed but this is not possible in general practice.

Another help in the differential diagnosis is the plantar response. Hart (154) has shown that a positive Babinski occurs frequently in cases of hypoglycaemic coma. Diabetic coma, unless accompanied by an organic lesion of the pyramidal tract, never gives an extensor response.

Beaumont and Dodds (155) consider softness of the eyeballs to be of great diagnostic importance.

Labbe (156) stresses the importance of Kussmaul's dyspnoea already referred to, as a diagnostic sign. It is always present in diabetic coma and never present in hypoglycaemic coma.

If diabetic coma is diagnosed the following line of treatment is carried out:

(1) If the patient has not been taking insulin, 30 units of insulin are injected; if the patient has been under insulin treatment, 50 units of insulin are administered.

Joslin (151) is conservative in the amount of insulin injected. Because of the recovery of many of his cases on small doses, he advises 20-40 units as an initial dose, to be repeated, half-hourly if necessary. Many authorities advise much larger doses.

(2) The patient is carefully observed and if no improvement takes place within half an hour the insulin dosage is repeated. The insulin is repeated half-hourly till improvement takes place.

(3) If the patient partially recovers and then relapses hypoglycaemia must be suspected, and the urine examined. Negative Benedict and Gerhardt tests indicate a hypoglycaemia and two ounces or more of

sugar must be administered immediately, if necessary by means of a stomach tube. Intravenous injections of sterile glucose are preferable but not always possible in general practice. Made up solutions are usually however, easily procured. If Benedict's and Gerhardt's tests are still positive then the half-hourly injections of insulin are continued.

Following Joslin's (158) advice, glucose is not given with the insulin as a routine measure. As the blood contains an excess of sugar it does not appear reasonable to administer sugar. Joslin states that he has not yet found that cases require more sugar than that already present in the blood to oxidise the ketone bodies.

Poulton and Payne (159) have pointed out that there may be a hyperglycaemia without a glycosuria due to defective kidney secretion, and Beaumont and Dodds (160) report a case where there were strongly positive Rothera and Gerhardt tests with a negative Benedict test. This patient had had sugar in his urine and had been suddenly deprived of carbohydrate food. His urinary sugar disappeared but his fat metabolism became so deranged that he went into coma.

In these cases the practitioner will have to be guided solely by Gerhardt's test. Blood-sugar estimations would be extremely useful in these cases. As a precautionary measure it would appear advisable to administer a corresponding number of grams of glucose to the number of units of insulin injected in these cases.

When the patient recovers consciousness and the sugar and ketone body tests are negative, then for the first 24 hours 50 grams of sugar controlled by insulin in four hourly doses are administered as advised by Joslin (161). Following this the patient is put on a Group "A" diet.

Accessory measures in treatment.

The patient must be kept warm. The patient is usually dehydrated by the polyuria and eight ounces of water should be given by mouth or stomach tube every hour. Tea and coffee are also freely given. An enema is given after the first dose of insulin has been administered, followed by the introduction of $\frac{1}{2}$ pint of normal saline in the hope that it will be retained and absorbed.

Sources of sepsis should be looked for and

treated as soon as possible. A septic focus may have been the deciding factor in the production of the coma. The presence of a raised temperature is of great help here for in a straight forward case of coma the temperature is always sub-normal. Where the temperature is raised or even normal, the teeth, tonsils, chest and abdomen should be carefully examined for a septic focus.

Cardiac stimulants may have to be given. Coma is extremely detrimental to heart cases.

Lawrence (162) points out that coma may be accompanied by anuria and is very fatal in these cases. The anuria may be due primarily to defective kidney function or it may be due primarily to a failing heart causing a lowered blood pressure.

A low blood pressure indicates severe shock and the patient is in danger of dying from circulatory failure. Graham (165) advises the intravenous administration of a pint of 1.2% solution of sodium chloride when the blood pressure is 70 mm. or below.

Labbé (164) points out that this cardio-vascular collapse met with in some cases of coma is due to a toxic inhibition of the bulbar vasomotor centre

producing vascular hypotension. He advises the administration of large and continued doses of adrenaline to counteract the vascular hypotonia.

Recovery from coma is very similar to a patient recovering from an anaesthetic. Respiration changes from the regular sighing type to the irregular noisy variety. The limbs begin to stiffen and the arms are waved about and gradually the patient becomes rational.

Alkali Therapy.

Concerning the administration of alkalis there appears to be a diversity of opinion. Maclean (165) in Edinburgh in 1927 stated that it was his rule not to administer alkalis, but later in London (166) in 1929, he stated that he administered small doses. Lawrence (167) and Cammidge (168) also advise the administration of small doses with the object of restoring the depleted alkali reserve of the blood.

Joslin (169) advises strongly against the use of alkalis in coma. He reports the case of a patient who developed alkalosis following recovery from coma to whom no alkalis had been given and he points out that, even when the alkalinity of the blood is brought back to normal by the administration of alkalis, coma persists.

Goldblatt (170) has carried out some interesting experiments on this subject. He induced a ketosis on himself by starving for 48 hours. 50 grams of glucose relieved this ketosis in one hour's time. He repeated the experiment but with the sugar he took a large amount of bicarbonate of soda. He found that the ketosis lasted for eight hours. He repeated the experiments on animals and found the same result. He thus proved that ingestion of large quantities of alkali prolongs ketosis.

Goldblatt then administered 30 grams of bicarbonate of soda to a case of severe diabetes without ketosis and he produced a ketosis thereby. This case was under insulin control and had not shown a ketosis for the previous year. He thus proved that the ingestion of large quantities of alkali inhibits the action of insulin.

Haldane and ^rWigglesworth (171) working on this subject found that overbreathing and bicarbonate ingestion in normal subjects produced ketonuria. The respiratory quotient was found to fall very low three hours after the bicarbonate ingestion. The sugar tolerance was also much lowered.

They then compared the effects of acidosis produced by ingestion of ammonium chloride. They found that there was neither ketonuria nor lowering of the respiratory quotient but there was a lowering of the sugar tolerance. They concluded that alkalosis checked the oxidisation of carbohydrates and acidosis hindered the storage of carbohydrates.

As it would appear that alkalis hinder carbohydrate metabolism it has been the rule in practice not to administer them.

Three cases of diabetic coma have been met with and treated in general practice during the past four years. Mr. C. who was on insulin treatment, developed coma on the day of return from a ten days holiday in London. Mr. B., and Miss J., who were not under insulin treatment, developed coma and were seen by the writer for the first time in this condition. All three cases were treated as outlined above and recovered. Mr. B., as previously stated in the Introduction, died from heart failure in eighteen hours time.

It might be stated here that the writer is of the opinion that it is very advisable for every

practitioner to carry a 5 c.c.tube of double strength insulin in his emergency bag.

(2) Pregnancy.

Pregnancy in a diabetic patient is commonly regarded as an extremely rare event. Walker (172) describes the treatment of a pregnant woman, the first to be treated at the Middlesex Hospital in a series of 10,000 confinements. Not a single case could be found in the records of the City of London Maternity Hospital among 27,567 patients confined. Lambie (173) points out that diabetic women seldom became pregnant because of the associated sclerotic changes in the ovaries and uterus. Smit (174) states that as high as 5% of diabetic women do become pregnant.

Diabetes may occur for the first time during pregnancy. Joslin (175) states that diabetes is more menacing to pregnancy than pregnancy is to diabetes. Lambie (173) shows that pregnancy aggravates a pre-existing diabetes and that the maternal and foetal mortality rate are high. Insulin has improved the prognosis, especially as regards the life of the mother. Hyperglycaemia in the mother leads to hydramnios in the foetus. The islet tissue of the foetus

has been shown to undergo marked hyperplasia and it is thought that improvement in the mother's tolerance commonly observed towards the end of pregnancy is due to insulin passing from the foetus to the mother. Lambie points out that there is no experimental evidence to prove this.

Blood-sugar estimations should always be performed as lactosuria and renal glycosuria may be present. Campbell and Macleod (176) state that renal glycosuria is relatively common in pregnancy.

In the treatment, the diet must contain a relatively high proportion of carbohydrates to avoid ketosis and Campbell and Macleod suggest a G: FA ratio of 1:1. Hypoglycaemia must be specially guarded against as it is a common cause of foetal death.

Lambie gives the following indications for abortion:-

- (1) Where the patient is unwilling to undergo continuous supervision.
- (2) Where the patient is emaciated.
- (3) Where there is a rapid loss of tolerance in spite of treatment.

(4) In cases of ketosis with uncontrollable vomiting. He advises Caesarean section under nitrous oxide and oxygen where a large foetus is expected.

During labour the usual doses of insulin with a liberal allowance of easily assimilated carbohydrate food should be given. Hyoscine and morphia narcosis should be employed.

Smith and Roques (177) point out that after delivery hypoglycaemic coma is very apt to occur and the insulin dosage and diet must be carefully controlled.

Gangrene.

Gangrene is the commonest condition requiring operation in the diabetic and was a common cause of death in pre-insulin days. It occurs almost exclusively in senile cases and affects the lower extremities. Joslin (178) shows from his statistics that 1 in 5 of his patients over 70 developed gangrene. In a recent paper on cholesterol Chamberlain (179) points out that the hypercholesterinaemia which occurs in diabetes is probably the causal factor in the production of arterio-sclerosis.

From experiments he shows that injections of insulin into a normal rabbit results in the marked decrease of cholesterol in the suprarenals. He assumes, therefore, that the suprarenals normally synthesise cholesterol under insulin control and consequently the absence of insulin in diabetes leads to an uncontrolled production of cholesterol.

Cambridge (180) has recently shown that, on the investigation of sixteen cases of retinitis, the most constant chemical abnormality found was the low calcium level in the fasting blood. He points out that there is experimental evidence that the metabolism of calcium and cholesterol are related, a fall of calcium in the blood being associated with a rise in cholesterol. Retinitis is invariably associated with arterio-sclerosis. In arterio-sclerosis calcification of the mesial layer of the arteries is the typical finding, and it would appear that the persistent lipaemia found with increasing frequency in elderly diabetics renders the arteries specially liable to a deposition of calcium in the mesial layer thus producing the condition of arterio-sclerosis.

Arterio-sclerosis is the most fateful complication of diabetes and its treatment consists primarily in its prevention which is obtained by maintaining a normal blood-sugar level at all times and thus obviating a hypercholesterinaemia. As already pointed out Joslin strongly emphasises the importance of keeping the urine sugar-free in all cases of diabetes for this reason.

The hygiene of the feet must be very carefully attended to. Joslin points out that if the elderly diabetic will keep his feet as clean as his face, then gangrene will seldom if ever occur. When gangrene is first observed a decision as to the treatment must be made immediately.

If the gangrene is moist, spreading and accompanied by constant pain, immediate operation is necessary.

If the local condition is dry and the urine contains sugar and perhaps ketone bodies, delay is permissible to try the effect of treatment.

Senile diabetics with gangrene respond less quickly to treatment than the young and require more insulin to obtain the same effect. (Lawrence (181)).

When operation is decided upon, then the precautions taken are as for any surgical emergency and are detailed later.

The writer has treated one case of diabetic gangrene. Mr. H., aged 65 developed gangrene in July, 1926. Examination of urine showed positive Benedict and Rothera tests and a negative Gerhardt test. Diabetes Mellitus was diagnosed and this was confirmed later by a blood-sugar estimation. The gangrene was of the dry variety and the patient was put on a Group "A" diet. He made a good recovery. His symptom of constant pain passed off four days after the institution of treatment.

Pre-operative precaution
in the diabetic.

Surgical operations in the diabetic as in other patients are either urgent or non-urgent.

If the operation is urgent then post-operative ketosis is the chief danger to be feared. The urine is tested for sugar and ketone bodies and a blood-sugar estimation is performed if there is time. If glycosuria and ketonuria are present, the patient

is treated practically on the same lines as are laid down for the treatment of coma, detailed above.

Lawrence (182) advises the administration of 20 units of insulin and 20 grains of sugar one and a half hours before the operation, to be repeated four-hourly after the operation has been completed. If there is not much sugar in the urine, then the sugar dosage should be double that of the insulin dosage. More heroic doses of insulin, up to 60 units may be required in severe toxic conditions. Each case will require careful individual treatment.

When the operation is not urgent, the treatment is the same as the routine treatment of diabetes. The patient should be brought to the operating table in a condition of normal metabolism.

Lawrence (183) advises that on the day of the operation, most of the fat should be omitted from the diet and the bulky carbohydrate food should be replaced by its equivalent of easily digested articles like milk, gruel, etc. There should be no starvation and no omission of insulin.

Local or spinal anaesthesiae are desirable if a general anaesthetic is necessary, chloroform should

never be used. Gas and oxygen is the anaesthetic of choice and failing this, Ether. With the advent of insulin, the mortality rate of the diabetic surgical case is now only slightly above that of the non-diabetic.

Other Complications.

All illnesses and infections change the condition of the diabetic for the worse, as they lower the carbohydrate tolerance and thus tend to produce ketosis. They temporarily change a mild or moderate case into a moderate or severe one. If the disturbance is slight it may only be necessary to restrict fats as much as possible. As already shown insulin may have to be used in cases where dietetic measures were previously sufficient.

Mrs. E., a patient on dietetic treatment alone developed a bilateral pyelitis in March 1926. She required 8 units of insulin twice daily during her illness. When the infection subsided she returned to her usual diet without insulin.

Lawrence (184) points out that in some cases after the illness has subsided the function of the pancreas may be permanently decreased and the original

balance of diet or of diet and insulin, may have to be altered.

Local Infections.

All septic foci, septic teeth, pyorrhea, boils, carbuncles etc., should receive immediate surgical treatment. At the same time the diabetes must be controlled by diet and insulin if necessary. Decided improvement usually follows the removal of septic foci.

Digestive System.

As already pointed out any digestive upset should put the practitioner on the alert for the presence of ketosis. If this is not present then most digestive upsets will usually subside with a few days in bed on a light fluid diet.

Diarrhoea is difficult to treat, especially in children. The usual treatment is rest in bed, abstinence from food, castor oil, and later opium.

Respiratory System.

Pneumonia and Tuberculosis are serious complications. Ample measured amounts of nourishment must be given and insulin in large doses may have to be given four-hourly.

In general the treatment of the complications of

diabetes consists in a modification of the existing diabetic treatment along with the usual routine treatment of the complication.

Cataract will require the treatment of an eye specialist.

Constipation.

Constipation has not been found to be a common complication in the writer's experience. As a symptom of the disease it is a constant feature but when treatment has been instituted constipation has been found to be the exception.

This is probably due to the excess of vegetables in the diet.

All patients are warned to avoid constipation.

Cases not responding to

Insulin Treatment.

Root (185) describes a case of haemochromatosis in which increasing doses of insulin up to 1,680 units a day failed to prevent death in coma. The necropsy revealed almost total destruction of the pancreatic cells.

Taussig (186) describes a case of a woman who

went into coma and a dose of 1,100 units did not effect recovery.

Labbé (187) is of the opinion that no case of true diabetes, however severe it may be, is refractory to insulin. He points out that in some cases of reported failure the trouble has been renal glycosuria without hyperglycaemia; in cases of coma that the failure of insulin has been due to cerebral haemorrhage or uraemia. He states that true diabetes complicated by severe infections is not refractory to insulin if only big enough doses are used.

Lawrence (188) disagrees with Labbé and states that for no known reason cases which are extremely resistant to insulin do occur. He describes the case of a boy aged 19 who required 400 units on a fixed diet to reduce the blood-sugar to normal. In his experience such a diet had never before required more than from 60-70 units daily, even in the severest case of diabetes. All the factors which are known to counteract insulin were absent in this case.

Insulin-Substitutes.

Several substitutes for insulin appear in current medical literature. They are synthalin, glukhorment, myrtillin, oxantin, glucosone and trypsogen, diatana and insulin tablets.

Synthalin.

Synthalin is the best known of these and reference to Joslin (189), Lawrence (190), Maclean (191), Labbé (192), and Rabinowitch (193) show that synthalin does act beneficially in some cases of diabetes. Its great recommendation is that it can be administered orally. It is a guanidine compound and was discovered by Frank (194) and has been used extensively in Germany. At a meeting of the Royal Society of Medicine, Dale (195) showed by experiments that synthalin reduced the sugar circulating in the blood but failed to produce storage of glycogen.

Lawrence, Cammidge and Graham took part in the discussion and the conclusions arrived at may be summarised as follows:-

(1) Glycosuria and hypoglycaemia are not diminished immediately but the action is definite after three days.

- (2) It will not relieve coma or ketosis.
- (3) It gives rise to gastro-intestinal disturbance due to its toxicity.

Reports of synthalin treatment from the leading hospitals of the country to the Medical Research Council (196) more or less confirm these results.

Glukhorment.

Glukhorment was introduced by Von Noorden (197) in 1927. It is stated to be a "strong tryptic digestion of fresh pancreas". Lawrence (198) has investigated ^{this preparation} ~~its action~~ and states that its action is the same as synthalin - namely, moderate reduction of glycosuria and hyperglycaemia and the production of toxic symptoms. Von Noorden (197), Schwab (199) and Rathery (200) quote good results and suggest its use along with insulin in severe cases and alone in mild cases

Myrtillin.

Allen (201) by experiments on dogs shows that myrtillin, a vegetable substance, gives superior results to insulin. It is given orally. Its action is less prompt, less powerful and less certain than insulin. Joslin (202) states that he tried it on

three patients but is not convinced of its efficacy.

Oxantin.

Oxantin is recommended by Bouckaert (203). It is a proprietary article and is administered orally.

Glucosone.

Hynd (204) found that when glucosone, one of the oxidisation products of glucose, was injected into mice, a condition similar to that produced by insulin injection took place. It gave a similar action when given by the mouth. Herring (205) points out that few attempts have been directed to ascertaining what form of carbohydrate other than glycogen results from the action of insulin upon glucose and if it can be established that glucosone is an intermediate substance then its importance in the treatment of diabetes is obvious.

Trypsogen and other

Proprietary Tablets.

Fuller (206) has recently carried out experiments with Carnrick's trypsinogen, Parke Davis's pancreatic extract, synthetic insulin tablets A and B and diatana tablets. He treated diabetic patients with all these tablets, keeping accurate and careful

records of the hyperglycaemia and glycosuria in all cases. He arrived at the following conclusions:-

(1) That the administration of oral preparations of the pancreas is a waste of time and is harmful to the patient by delaying the proper treatment.

(2) That in those patients on whom blood-sugar curves were taken over several hours no definite difference in the mean blood-sugar level could be detected as the result of treatment with oral preparations.

(3) That the only benefit the tablets possess is that some patients, if placed on a strict diet alone, feel they are not receiving proper treatment and the giving of these tablets obviates this difficulty. Unfortunately this has been found to be only too true in general practice.

In January 1926, the writer tried the effect of trypsin tablets on Mrs. E. They were found to be of no value at all. Probably in those cases of reported success the accompanying dietary restrictions has been solely responsible for the improvement.

The view that insulin is the only successful substance in the treatment of diabetes mellitus is generally held by the experts of this country and of America.

Use of Insulin in conditions

other than Diabetes Mellitus.

The application of insulin to conditions of non-diabetic origin has attracted the attention of investigators throughout the world. Already the literature ^{which has} sprung into being on the subject is formidable.

Insulin has been employed in cases of malnutrition, tuberculosis, pernicious anaemia, psoriasis, sea-sickness, cyclical vomiting in children, toxaemias of pregnancy and many other conditions. From a perusal of the literature of these cases, the results appear to be satisfactory, especially in the cases of the toxaemias of pregnancy. Most of this experimental work appears to have been carried out in America and on the Continent.

Four cases of toxic myocarditis were treated with glucose and insulin by the writer in the winter 1928-1929. The works of Visscher, Muller, Marks and Bodo stimulated this line of treatment. Visscher and Muller (207) showed that in a heart-lung preparation commercial insulin caused a transitory increase in the power of the muscle fibres and Bodo and Marks (208)

found that when a mammalian heart was perfused with sugar the disappearance of sugar was accelerated under the action of insulin. They concluded that the insulin caused the glucose to be stored up in the muscle fibres as glycogen. Three convalescent cases of influenza and one of pneumonia were given 5 units of insulin half an hour before the two main meals of the day. During the meals the patients took two heaped tablespoonfuls of powdered glucose. The nurse in charge administered the insulin and glucose. An improvement in the pulse rate was noticeable in all cases. It cannot be claimed that the improvement was due entirely to the insulin but theoretically the procedure appears to be sound. On account of the difficulty of administering insulin, this procedure cannot be recommended as a routine treatment in practice but in those cases of severe myocarditis following infections, the procedure is recommended.

SUMMARY.

In this thesis an attempt has been made to show how the general practitioner may diagnose and treat his diabetic patient in the most efficient manner. In the writer's experience no other condition met with in practice demands the same degree of knowledge and patience, offers the same degree of success and earns the same degree of gratitude from the patient as does ^{the treatment of} diabetes. The co-operation of the patient is required more in this disease than in any other, and, as the diabetic is ^{almost} invariably an intelligent one, this is obtained in most cases in a whole-hearted manner.

The conclusions arrived at from the study of current medical literature on diabetics and from observations made in practice may be summarised as follows:-

1. A study of diabetes emphasises the fact that the greatest single factor in the promotion and maintenance of good health is a proper diet both from the quantitative and the qualitative points of view.
2. In the production of diabetes mellitus it is suggested that two factors are always present. It is thought that obesity, an infection, heredity or any

other recognised associated condition merely acts as a predisposing or exciting factor and that a "specific factor" is also present in every case of the disease. It is further suggested that this "specific factor" may be ^{an} ultramicroscopic virus with a special affinity for the islet tissue of the pancreas.

3. The early recognition of diabetes, as of all other diseases, is of great importance, and for this reason the early manifestations of the disease should be familiar to all practitioners.

4. A yearly medical overhaul of each of his patients is advocated. It is felt that, amongst other conditions many cases of early diabetes would be detected in this way, and consequently a much better prognosis would result.

5. Every case of glycosuria met with in practice demands a careful systematic search for the type of sugar present and the cause.

6. Only the suspicious case of diabetes requires the performance of the sugar tolerance test. It is generally accepted that a fasting blood-sugar of $.13\%$ or over; or a blood-sugar figure of $.2\%$ or over one hour after a meal (except in the aged or in the

presence of such organic diseases as hyperthyroidism; hyperpituitarism, etc.) denotes true diabetes mellitus, and sugar tolerance tests should not be performed in these cases.

7. The prognosis of diabetes more than that of any other disease depends on the treatment and the success of the treatment depends on the zeal of the doctor and the perseverance of the patient.

8. It is thought that the term "arrested" instead of "cured" might be used with advantage in those cases becoming sugar-free under treatment.

9. It is considered that the optimum diet for the diabetic is the minimum one which will sustain his strength, at the same time keeping his blood-sugar level within normal limits, to which end insulin may have to be employed and if employed then a minimum amount of insulin to achieve this purpose should be administered.

10. The careful regulation of the food intake still remains the most important factor in the treatment of the diabetic.

11. The aim and ideal of diabetic treatment is to keep the blood-sugar within normal limits and the

urine sugar-free at all times, thus allowing the pancreas to regenerate and also preventing the occurrence of complications.

12. Every patient who is having insulin should receive in the process of determining his insulin dosage an overdose of insulin for two purposes. Firstly to establish his insulin level, and secondly to familiarise him with the symptoms of hypoglycaemia.

13. The early clinical manifestations of ketosis are of great importance to the practitioner; firstly as a means of preventing the onset of coma in a known case and secondly as a means of recognising the presence of severe diabetes in an undetected case.

14. Coma demands immediate treatment. Experience shows that the longer the patient remains in coma untreated, the more difficult it is to revive him.

15. As it appears that the administration of alkalis hinders carbohydrate metabolism, their use in cases of ketosis is discountenanced.

16. The importance of every general practitioner carrying a 5 c.c. bottle of double strength insulin in his emergency bag along with his Benedict and

ferric chloride reagents is emphasised.

17. Expert opinion in this country and in America considers that insulin is the only successful drug in the treatment of those cases of diabetes which do not respond to dietetic measures alone and in all cases of ketosis. Without exception insulin substitutes are inefficient.

18. In spite of the increasing incidence of diabetes mellitus, dietetic measures and insulin are controlling the disease; and, by restoring health to the mild and medium case and by saving the life of the severe case, the lives of many useful citizens are annually preserved.

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