Diabetes Mellitus; its Pathology, Complications and Treatment.

Joseph E. Rogers.
(M.B. C.M. 1893)
New Zealand.
The disease Diabetes Mellitus, from time immemorial has been one of the most inconstant of diseases. Autocles, who is said to have lived in the first century, knew the disease by name, which, it now seems, was described accurately by him in the second century. The cause of the disease, yet it was not until 1674 that the cardinal feature of the disease, viz. sugar in the urine, was discovered by Sir Thomas Willis. Willis' discovery was ignored until 1775, when T. Dobben of Liverpool confirmed Willis' conclusions by the evidence of sour fermentation and the character of the residue from evaporation of the urine. Dobben also stated that sugar existed in the blood of diabetics as well as in the urine but he relied on the property of taste. Cruikshank was the first to devise a chemical test which consisted of the action of nitric acid in converting it into oxalic acid.
recognizing it by the form of the crystals. The presence of sugar in diabetic fluid was disputed until Ambrosoni and Newland succeeded in separating it. They began in obtaining evidence of fermentation with yeast.

Little advance concerning the nature of the disease was made until the middle of the present century when Claude Bernard propounded his Hyposemic theory, which gave increased impetus to those investigating researchers in this direction.

In the past, all sorts of vague ideas have existed as to the nature of the disease yet it must be admitted that even now opinions are by no means settled concerning the essential features of this baffling disorder. As it is only through physiology that we can attempt to arrive at well-founded pathological conclusions, it is my intention in these pages to give an outline of the physiology of the disease, then
to turn to the pathology, finally to give a few general considerations concerning the treatment of the disease. As the carbohydrates play the chief role in the disease, the following classified according to their chemical formulae, are the ones which are chiefly taken in as food and consequently those which will be considered here.

The amyloses \((C_6H_{10}O_5)_n\) such as cellulose, starch and glycogen.

The saccharoses, \(C_{12}H_{22}O_{11}\), maltose, lactose and cane sugar.

The sugars \(C_6H_{12}O_6\), dextrose, lactulose and galactose.

We have now to trace the carbohydrates from their introduction into the buccal cavity until they pass from their alimentary canal into the portal vein. The first change which takes place occurs in the mouth where the starch comes in contact with the saliva, an alkaline secretion containing an unorganised
Ferment known as salivin; by its action starch is finally converted into maltase and dectin (a small amount of glucose may be formed at the same time); during the process several intermediary products are said to be formed viz. Amylo-dextin, erythodextin, and amylodextin. The equation which represents the change is probably this:

\[ 10(C_6H_{20}O_10) + 8H_2O = 8(C_6H_{22}O_{11}) + 2(C_6H_{22}O_{11}) \]

Sol. starch \[\rightarrow\] maltase \[\rightarrow\] amylodextin

The extent of change effected by the saliva is probably small owing to the short duration of contact between the ferment and the starch.

The food is then passed along the oesophagus into the stomach, where it comes in contact with the gastric juice which checks the diastatic action of the saliva.

Cane sugar is said to be converted into glucose to a slight extent in the stomach as shown by the following experiment: A solution
of cane-sugar was introduced into the thoroughly cleansed stomach of a recently killed rabbit. The stomach was ligatured at both ends and placed in a beaker of water at 118°C for 24 hours. At the end of this time the water was examined and found to contain 9% of glucose while the liquid in the stomach was found to contain 24% of glucose. (Pavy, Physiology of the carbohydrates.)

The action is said to be due either to the gastric juice or to a soluble enzyme which exists in the stomach walls, but some change may take place in the living cells; in fact, the action may be due to fermentative changes. Lactase is also said to be converted into glucose—

As the stomach is capable of retaining diffusible substances, the absorption of glucose, if any be formed, will take place. The food then passes into the alimentary canal and comes in
contact with the bile, pancreatic juice & secreta enters actively. Yet it is through the influence of the last two that the conversion of the carbohydrates into the form in which they are absorbed by the intestinal blood takes place. The pancreatic juice contains a ferment amylopectin which has a characteristic action as in the case of the saliva, but the conversion of the starch into maltose takes place more rapidly & to a greater extent. Glycogen is changed into dextin & fructose sugar (as glycogen is the animal analoge to starch, what has been said about the latter will hold good for the former) & maltose is slowly changed into glucose, but cane sugar is not affected. Bile, beyond neutralizing the acidity of the chyme from the stomach & so assisting starch digestion has no effect on the carbohydrates.
The food in the intestine also comes in contact with the intestinal juice derived from Brunner’s and Lieberkühn’s glands but mainly from the latter. The secretion from Brunner’s glands is said to have a diastatic action to convert maltase into glucose; but owing to the smallness of quantity of the glands their secretion cannot properly be obtained as considerable uncertainty exists with regard to its action.

The “pancreatic juice,” on the other hand, has two chief actions on the carbohydrates:

1. It continues the action of the saliva and pancreatic juice by converting maltase into dextrose.

2. According to Claude Bernard, it contains a ferment “invertin” which converts cane-sugar into dextrose and levulose. Thus:

\[ C_{12} H_{22} O_{11} + H_2 O = C_6 H_{12} O_6 + C_6 H_{12} O_6 \]

cane-sugar dextrose levulose

(Sandri’s printing 1978)
The action is a gradual and continuous one, and depends on the amount of ferment present at the time it is allowed to act.

Although the secretions from the small intestine effect a change on maltose by converting it into dextrine, it has been found by experiment that an extract of the tissue of the small intestine itself rapidly converts maltose into dextrine; much more so than the secretions of the small intestine.

(Brown and Neum Wire Rev Soc 2040 393 588)

Lactose by the action of the "succus entericus" or by an enzyme existing in the alimentary canal is converted into dextrose and galactose thus:

\[
\text{C}_12\text{H}_{22}\text{O}_{11} + \text{H}_2\text{O} = \text{C}_6\text{H}_{12}\text{O}_6 + \text{C}_6\text{H}_{12}\text{O}_6
\]

Lactose  dextrose  galactose

Proof of the possibility of this is afforded by the fact that if lactose is given to the diabetic it appears as glucose in the urine.
Cellulase though little is probably digested in the human subject is chiefly interesting from the fact that it is digested in the alimentary canal of herbivora.

As regards its digestion in herbivora, it may be due to an enzyme but as yet no such enzyme has been proved to exist. It also may be due to the presence of putrefactive organisms in the alimentary canal splitting cellulose up into marsh gas and carbonic anhydride, as this occurs when sewer slime comes in contact with cellulose. This seems to be the more feasible theory as marsh gas occurs in the large excreta of herbivora and it increases in the intestine of man when largely fed on a vegetable diet. (Sheridan 1858, "Chemical Basis of the Animal Body")
The alimentary canal and by this means some of the sapajc may be disposed of. Bacillus acidolactici splits up cane sugar into lactic acid:

\[ C_6 H_{12}O_6 = 2(C_3 H_6 O_3) \]

Lactic acid.

Butyric acid fermentation also takes place and by this means sugar is converted into the fatty acid group and may become fat but the formation of fat probably takes place in the tissues of the body. The equation which represents the change in butyric acid fermentation is this:

\[ 2(C_3 H_6 O_3) = C_4 H_8 O_3 + 2 CO_2 + \text{H}_2 \text{O} \]

Lactic acid. Butyric acid.

From the above observations, it will be seen that the carbohydrates in the alimentary canal are converted into glucose which is absorbed by the blood vessels and carried to the liver by the portal vein.
The sugar thus absorbed is stored up as glycogen in the liver which was discovered by Claude Bernard in 1857. He then traced the sugar through the circulation and discovered by analysis more sugar in the hepatic veins than in the portal and this led to his glycogenic theory. As glycogen plays an important part in diabetes it will be as well to give some of its chief characters etc.

Glycogen (C6H10O5)n is a carbohydrate from its similarity to starch is often called "animal starch"; it occurs to a great extent in liver, but also in muscles, white blood corpuscles, gills, corpuscles, in all the tissue of the body of the embryo during foetal life, in the testicle, cartilage, in large quantities in many molluscs. It is said to occur in the hair of man in diabetic coma.
When pure, it is an amorphous white powder, it forms an opalescent solution when boiled with water, is precipitated by 60% of alcohol, and when treated with mineral acids forms ecretin & finally dectin, if treated with pancreatic & saliva secretion, malt not decline is formed, it can be prepared & extracted from the liver of rabbits fed on carrots.

If the liver of such a rabbit be cut out & half of it rapidly thrown into boiling water, the other half left, after a short time the liver not thrown into boiling water will be found to contain much sugar & little glycogen, while the other half will contain little glycogen & much sugar. From this it was inferred that a special enzyme existed in the liver capable of transforming glycogen into sugar, but no such enzyme has been found to date to do the change.
is probably due to some action of the cell.

The glycogen of the liver as we have seen is derived chiefly from the carbohydrates, but for that, mucin, gelatin & fats have also been said to give rise to it.

As regards gelatin (Landois & Sterling, Physiology 3rd edit 1863) Voit has shown that when administered it acts like fats and carbohydrates as an "albumin sparing" substance. For instance, the carnivora when fed on a flesh diet can maintain their metabolism in equilibrium if gelatin is added to the food. As regards mucin some considerable doubt exists. Sandwehr in his researches on mucin obtained a substance which he called "animal gum" from its similarity to vegetable products of the same name. Although this body with acids yields a reducing sugar yet it is not altered by the saliva &
Franceniacie juices, as on the print the evidence is not conclusive (S. Lea Chemical Basis of animal body). Proteid also are said to give rise to if a starved animal kept exclusively on meat diet glycogen is found in the liver but the objections to this are (Paton Physiology Book II p. 751 Edit 4th). Quantities of glycogen thus stored up is much less then when carbohydrates are given.

Ordinary meat especially horse flesh on which dogs in these experiments are usually fed contain a certain amount of glycogen. Again when dogs are fed on purified proteid such as albumin casein the quantity of glycogen become still smaller.

It seems proved however that proteid can give rise to carbohydrates for D. Paton (F.M.T. Dec/1914 Pflz) says "when an animal has been deprived of
of all its glycogen an enormous sugar formation with a corresponding desintegration of proteids may be produced by the administration of phenolizine, and that in an animal deprived of "its glycogen by phyllo-knine poisoning this carbohydrate appears again in the liver and muscles under the influence of chinin even though the animal be starved." Fats are also said to be converted into carbohydrates in the liver, but if an animal be fed entirely on fats no more glycogen is discovered in the liver than in the case of the retaining animal. Ray (Physiology of the Carbohydrate, p. 51) maintains that "proteids contain a carbo-hydrate molecule which under certain conditions can be 'cleaved off' from the former. This carbohydrate, Ray says, gives reducing reaction with ammoniated sulfure oxide.
yield a crystalline residue with phenylhydrazin gives naphtol and tymol reactins with sugar, but this carbohydrate does not react in optical activity or fermentability, and moreover other substances besides carbohydrates give reaction with phenylhydrazine. So, as regards the source of the glycogen, we may come to the conclusion from the evidence brought forward that the carbohydrates of the food are the chief source, but in cases in which the carbohydrate are unable to maintain the portion of sugar in the outflowing blood at the normal height, the deficiency is probably made up from the protein, possibly from the fats.

As regards the manner in which the glycogen is deposited in the liver cells, two views are entertained viz., that the glycogen formed from the injection of carbohydrates...
formed by simple dehydration of the sugar brought by the portal blood or secondly, glycogen or some other carbohydrate material is a normal product of the metabolism of the hepatic cell. In the latter case the glycogen cannot be formed from dehydration of sugar. The process must be more complex. But it is supposed to be due to the splitting up of protein into sugar. In severe cases of diabetes when all carbohydrate food is withheld sugar still appears in the urine. The above is said to be the explanation. The same thing may take place in the formation of fat, protein on its way to from meat is split up into meat and a carbon body which may be retained in the body in the form of fat, but it does not follow that if proteid metabolism gives rise to glycogen the process
must occur in the liver, it may take place in other parts of the body—the muscles for instance. In the evidence given (Starling's Physiology Part II 759 6th Edit) we must incline to the belief that glycojen is formed from the dehydration of carbohydrate, for if it were due to a splitting up of protein constituents the glycojen deposited in the liver ought to bear a certain proportion to the amount of mea in wine, but this is found not to be the case. If an animal be starved and then fed on disclose the amount of glycojen found in the liver within a few hours as compared with the amount of mea in wine is too much to be accounted for by the above theory. If palaetra be given at present distinction exists, but we have special evidence to prove whether palaetra is formed into deacine
in the alimentary canal.
Again the dehydration theory may be supported by what is seen to take place in vegetable cells which can convert starch into sugar. Sugar into starch if vegetable cells can accomplish these changes is it not reasonable to suppose that animal cells can also accomplish them?
Again if sugar be injected into the jugular vein it appears in the urine but if injected into portal vein it does not appear in the urine, even if greater quantities are injected than in case of the jugular vein.

We have now to discover what is the destiny of this sugar. The glycogenic theory implies that during life the sugar in the liver is being converted into sugar, but the process is supposed that only sufficient to supply the needs of the body is liberated.
Pavy denies this in his work (Physiology of the Carbohydrates P226) says: "The liver in fact instead of doing what is claimed for it under the phlogenic theory doctrine does exactly the reverse. It sends the forms sugar to be discharged into the general circulation & conveyed to the tissues, an temporary store up carbohydrate material from ingestion to be subsequently allowed as much to pass on. On the contrary it keeps the general circulation free from sugar which would otherwise enter & show itself in the urine. Its office is an arresting one in relation to carbohydrate matter if it were not for the exercise of this office we should all be in the same position as the diabetic." He bases his argument chiefly on the analysis of the blood of the portal and hepatic veins, but these
analyses must be received with a
certain amount of caution as
changes may take place in the
blood after being withdrawn from
the body. Pavy says the hepatic
vein contains less sugar than
the portal but Bernard & mne
always observed maintain the
opposite theo.

Sweegen Pavy

Analysis of Portal Vein 0.119 1.5 to 4
Hepatic Vein 0.23 0.6 to 1

The blood in Pavy's analyses was
taken from the right side of the
heart while in case of Sweegen's
from the hepatic veins.

1. P. F. Paton in an article in the
(Etinburgh Med. Journal 1894)
denies the theory of Pavy & says
that the analyses of the head
blood & portal blood were not
had at one & the same time.

2. Animal was dead & change
may occur in the blood.

3. Portal blood is diluted with
blood from rest of body.
Swegen also found sugar in the hepatic vein after chloroform, curare, and morphia. Bock and Hoffman have succeeded in excluding the liver from the circulation in dogs, the blood became free from sugar. Again Minkowski taking advantage of the communication between the portal and renal vein in the jeece excluded the liver from the circulation and found that the blood became free from sugar. It Nation also says that Dazy's method of abstracting sugar with alcohol cannot be relied on as all the sugar is not removed. By using potting alcohol the sugars less soluble in alcohol are not taken up, if weak alcohol is used some of the lower alcohols are taken up.

As regards these analyses...
considerable difficulty exists because in the quantity of blood flowing through the liver at any given time might contain such a small amount of sugar as not to be determinable by analysis; yet, if all the blood that passes through the liver at any given time were taken into account, the sugar thus present might account for the amount of glycogen present in the liver at any given time.

Another view which has been put forward is that the glycogen is deposited in the liver as a store of carbohydrate material to be drawn out as required by the animal economy. The blood always contains in normal conditions a certain quantity of sugar but it is necessary for this amount to be constant for if sugar...
increases in the blood an effort is made by the kidneys to get rid of it. The cells of the liver may in certain cases when too much carbohydrate material is being taken up the carbohydrate in the liver as glycogen, if this present too much sugar from setting into the circulation, but when carbohydrate is being taken, the percentage of sugar is kept up in the blood by the glycogen becoming reconverted into sugar. Glycogen, as we have seen, is found in the situations than liver, pig muscles especially, skeletal muscles, in the muscles of the embryo, where the glycogen is present in large amount when the muscles are undergoing situation & the glycogen in the liver cells is small in amount, but as the muscles become situated the glycogen disappears & becomes placed
up in the liver. In the muscles of the foetus it helps to transform the protoplasmic cell substance into a treated contractile muscle; in these cases also the glycogen acts as a store of carbohydrate material.

(Proteus. Physiology Text I. 1764 Ed ed. vii) It is also found in the epithelial cell, which lies between the maternal and foetal structures, also in rapidly growing cartilage and muscle. In these situations also it acts as a store of carbohydrate material.

In diabetes also it is found in the brain where it can be drawn upon as the tissues require. Again that the glycogen acts as a store of carbohydrate material is strongly supported by what occurs in the vegetable kingdom where the starch of the leaves is converted into sugar and carri

...
down to the roots where it once
mune becomes changed into starch.
We have now to see what becomes
of the sugar which is derived
from the liver to supply the needs
of the body.
Glucose as we have seen is
always present in small
quantity in the blood. Experiments on animals it has
been shown that the venous
blood coming from muscles
contains less glucose than the
arterial blood. The difference
is increased by contraction of
muscles also been found that by
taking a small quantity of
sugar the power of muscle is greatly
increased and the effects of fatigue
shortened, so, according to the
above it is to be inferred that
glucose contributes in some
measure to the nutrition of
muscle.
It has been said that the
Sugar is oxidised in the blood, but if sugar be mixed with blood and kept at the temperature of blood for some time no oxidation takes place. (Fothergill's Physiology Part II 1812, Edit 6th) and in the frog by replacing the whole of the blood of the body with a saline solution the metabolism of the body goes on just as well.

Also if easily oxidised substances such as pyrogallic and nitric acids be injected into the blood they pass out by the urine for the most part unoxidised.

The acid reaction of muscle is said to be due to the formation of pyruvic acid which is said to be derived from the glycogen stored up in the muscles. During activity glycogen disappears from muscle and lactic acid is formed but it is known...
that a muscle becomes acid when free from glycogen or glycogen probably does not serve this purpose. The lactic acid is probably carried to the liver where by synthesis it may give rise to glycogen, but in the liver it is probably oxidized into carbonic acid and water. (See "Chemical basis of the animal body" p. 120.)

The chief use of the sugar seems to be as a source of muscular energy, for here we find that there is a great increase in the amount of CO₂ given off in 2.0 of men as anaerobic materials must be the source of energy and the carbohydrates are supposed to give rise to it.

We have seen in the preceding phase that glycogen diminishes in muscles during muscular work and is stored up during rest. Kulp also found that in
Dogs glycogen disappears from the liver during work. Pavy (Physiology of the Carbo-
hydrates p. 233) denies, as we have seen before the theory given above says the liver
acts as a barrier to prevent the sugar entering the general circulation. He gives the
ultimate fate of the carbohydrates in the body as, in
part to be stored up as
glycogen, in part to be
converted into fat and get
again in part to enter into
the formation of protein
matter. He bases his theory
on having seen fat in the
epithelial cells of the
intestinal villi. These cells
being according to him the
agents by which the above is
produced after feeding
rabbits with rats, but it
does not follow that the fat
is derived from oats; moreover, other substances may be stained with eromic acid.

Pavy also relied on the above from his estimation of the analysis of the blood of the juntal hepatic veins, but, as we have seen before this cannot be relied on, as other observers throw doubt on his methods of analysis.

If we now trace the exccycle we find it is absorbed and enters the blood, so to a great extent printed as glycogen in the liver is consumed by living muscle it is discharged as carbmal acid and water.

**Necrosis Anatomy.**
The blood is sometimes described as being loaded with fat, a white cream-like layer floating on the coagulum after being drawn.
She red corpuscles are sometimes found to be broken down into a granular mass; Sabriul-Kheuy has shown that the polynuclear leucocytes often contain glycogen (Oster, The Triumphs of Practice of Medicine 1891 p. 297.)

Sugar in the blood is variously quoted thus -

<table>
<thead>
<tr>
<th>Name</th>
<th>Part per cent</th>
</tr>
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<tbody>
<tr>
<td>Pady</td>
<td>0.078 to 0.081 dog</td>
</tr>
<tr>
<td>6th</td>
<td>0.10 &quot; 0.14 &quot;</td>
</tr>
<tr>
<td>Sweegen</td>
<td>0.15 &quot; 0.19 man</td>
</tr>
<tr>
<td>Sherichs</td>
<td>0.12 &quot; 0.13 &quot;</td>
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The alkalinity of the blood-venous is reduced owing to the presence of organic acids in the blood such as diacetic acid & beta-pyruvic acid. Acetone is also said to exist and to the presence of those in the blood diabetic coma has been imputed.

Various changes in the nervous system have been described but the most constant seem
to be small cysts in the white matter which are quite free
from haematoxylin staining.

(Bradshaw Lecture on Medical
Anatomy of Diabetes Mellitus.
Saudley B.M. J. 1890 P. 438. Aug. 23)

These cysts have been found in
the medulla, frontal to be from
chroid plexus and have been
attributed to a failure of
nutrition. Dickinson has

described enlargement of the
perivascular spaces, the common
place to the centrum ovale or
the white matter in connexion
with some of the lower
convolutions, this enlargement
is said to be due either to
shrinkage of the brain tissue
and erosion of their walls or
expansion of their cavity in
connexion with mobil action
on the part of the contained
vessel. (Dickinson. "In Renal
& Chinary Affectin." Diabetes 1877 P. 398.)
Besides these, other changes have been noted such as tumour of the medulla, the presence of colloid masses thickening (Abraham, O.S. Dub. Med. Journ. Vol LXXXVIII P. 395). Haemorrhages in the brain substance do not appear to be common. Scurvyly out of 27 cases of cerebrospinal fluid the brain to be normal only in five. Almost all the above changes have been found in the spinal cord and diabetes occurs after injuries to the head and spinal column, also in some cases of locomotor ataxia and paralysis, and it has been found that the disease follows division of the spinal cord opposite the second dorsal vertebra.

In 3 cases (Harley, Henriot French) fundus pessary on the vagus nerve were discovered.
In the sympathetic system the chief change seems to be
enlargement of the semilunar ganglia (Bradshaw Lecture on
Mential Anatomy of Diabetes,
Mellitus, Sandly BM Jour 1890
P. 4130. Aug 23rd)
Duncan discovered this in 1878
and Sandly found it in
three of his cases.
Hale White (Path Doc Trans
Vol xxxvii P 67) has also described
similar lesions of these ganglia.
Other instances of thickening,
fibromatosis, sclerosis of the
sympathetic ganglia with
atrophy of their nerve cells
have been alluded to.
Cavazzani (Centralebl f. Algem
Part. Jul 1893, Brit Med Jour
Vol 12 Semtome 1893 P 28).
Wellesly an interesting case of
diabetes mellitus where the
above changes were markedly
visible while the pancreas
was not decreased. All the cervical and sympathetic ganglia showed some congestion of their blood vessels, increase of connective tissue and atrophy of the ganglionic cells. Microscopically, the ganglia showed atrophy, pigmentary degeneration, and necrosis of the nerve cells with increase of connective tissue and nuclei. Clinical observation has revealed the existence of a neuritis which may be multiple or attack particular nerves.

The heart in most cases is described as pale soft. Soundly found this condition in 40% of his cases, as the most common condition seems to be a fatty change. Others again say that hypertrophy is the most common change. Israel found it in 10%. Major
Samally both in 13\%, the hypertrophy is probably due to increased work thrown on the kidneys or else from the diminution of sugar circulating in the blood. The condition of the heart will depend partly on the condition of the patient in the late stages of the disease where there is marked wasting and the change will be the rule. While in the earlier stages hypertrophy, muscular lesion does not appear to be common, Samally only found this lesion in 1 in 29 and Winde only found it in 1 in 924 (Dub Jour of Med. Le. 1888. Vol LXXXV. O112).

The stomach and intestinal canal present little beyond the ordinary signs of intestinal catarrh, viz. thickening, mammillation, relaps, pigmentation, eczema, and
ulceration, however, never occurs.
The liver has been described as
healthy, but this appears to be
an erroneous view. There is
generally enlargement present
due to venous hyperaemia.
Rokitansky found the liver
in 15 out of 30 cases to be
enlarged, hyperaemic, hard, &
a dark-brown colour with its
acini imperfectly defined.
(Swain, Dictionary of Medicine Vol 2
1846, p. 456)
M. Franz, Elenard observed in
private practice at Vichy
that out of 324 diabetics,
hypertrophy of the liver was
present in 34.8% while in
23.7% there was induction of
the liver. The hypertrophy was
generally limited to the
right lobe. (Brit. Med. Jour
1840 Vol 11 July 12 1840).
Early degeneration of the liver
has also been described.
Hanot I. Schachman have described a kind of interstitial hepatitis which is often present.

May go on to cirrhosis, the lesion begins around the radicles of the hepatic vein and the condition is often associated with atrophy of the skin (Arch de Physiol 1886 Vol 7 p 50).

The liver has not been found to contain a great deal of fat. Meyl (Archiv Vorsch. Archiv B xcv 0. 36) give as their analysis:

Normal liver 3.70% per mille
Diabetic " 3.75 " "

Respiratory System:
The lungs are frequently diseased. The changes include all stages from acute to chronic pneumonia to the formation of cavities and gangrene. Kohlraush found them normal in only 7 out of
30. Diphtheria only twice out of 29. Scurvy but of 29 cases only 17.1% or 27%.  
Rheumatism was present.

Dreschfeld (Med. Chronicle. Vol 1, p. 5) describe the following types of lung affection in diabetes—
1. Acute Croupous Pneumonia—Very acute & fatal but rare.
2. Acute broncho-pneumonia which may terminate in gangrene.
3. Chronic caseating tubercular broncho-pneumonia; the commonest.

5. Gangrene of lung.  
Fat Embolism has also been described. It is here is been ascended the cause of coma, 
but this is probably a post-mortem formation due to the running together of the fat 
which was previously held suspended in a molecular.
state. The pneumatic change has been ascribed to the race-haune condition of the blood, but the race-haune blood does not seem to affect the other tissues to any great extent. The change must also be attributed to the nervous system, but in all probability it is due to the malnutrition which exists in thus renders the lungs more liable to the inroads of the tubercle bacilli.

Kidneys. The most common condition seems to be a slight degree of fatty degeneration (Saunderly Bradshaw Lecture on Diabetes Mellitus, B.M.J. 1890, p. 1439, Aug. 23). Saunderly found in his 29 cases not one of the kidneys normal. In this case the kidneys are generally enlarged and their capsules adherent.
of this organ.
In the majority of cases it appears to be atrophied, \textit{Sanareaux} found that in 9 out of 15 cases of typical wanting diabetes it was shrunked. (Bradshaw Lecture on "Massie Anatomy of Diabetes Mellitus," Saunders, But Med. Jour. 1890 P. 437. Aug. 23) Dr. Bull of New York experimented the pancreas in one of his patients with the result that the patient died of diabetes. Diabetes has also been found associated with cancer, pancreatic calculi, celiac, & cysts of the pancreas.
Various theories have been put forward to account for pancreatic diabetes, but they will be referred to mine particularly under the pathology.
Heyden & Lipse have since also extrapolated the pancreas & they found diabetes mellitus invariably
followed.

J. Vaughan Harley performed a large number of experiments on animals by extirpation of the pancreas in dogs with a like result. ("Experimental Pathological Evidence proving the existence of Pancreatic Diabetes", Journal Am. Physiol. Vol xxvi (204 1892).

According to Saunders (Bradshaw Lecture on "Malignant Anatomy of Diabetes Mellitus", Brit Med Jour Aug 23 1890 IV 138) the pancreas in the early stage is swollen from abundant infiltration of its tissue with round cells. In a later stage the gland shows a great increase of connective tissue and a hyaline degeneration of the glandular epithelium. The portion of gland thus affected seems to be converted into swollen masses of translucent material containing a few pale nuclei.
Pathology.

Before proceeding to the subject of diabetes mellitus, it would be as well to refer to the condition known as temporary diabetes or glycosuria.

The liver is supplied with nerves from the hepatic plexus, which takes origin from the celiac plexus, and its branches run in the portal canal with the hepatic artery and portal vein. It consists partly of medullated and partly of non-medullated fibers. The fibers of the hepatic plexus supply the hepatic artery, its branches, also the bile ducts and the gall-bladder. Vaso-motor fibers are also present to supply the branches of the portal vein, and it is also required that some of the fibers are directly connected with the hepatic cells. (A Short Book of Physiology, Foster, Part II, p. 66, 1893).
Into the solar plexus. The right vagus sends the greater part of its fibers to the splanchnic nerves (major and minor) end; the left vagus is also connected with the solar plexus but besides this sends a distinct branch to the hepatic plexus. Besides these other fibers form the spinal cord may pass through the sympathetic chain in the solar plexus.

Claude Bernard while on the subject of glycogen discovered that by transecting the spinal bulb of a well-fed rabbit close to the vesci-motor area that in a few hours the urine contained sugar which passed off in a few days. If the rabbit is starved little or no sugar appears in the urine. Conversely the better fed the rabbit the larger the amount of sugar in the urine while at the same
Since the glycogen in the liver disappears, it seems to prove that the sugar is derived from the glycogen of the liver.

The fact which the fiber travels to the liver has not been worked out, it does not travel by the vagi or splanchnic nerves. In with division of these nerves the artificial diabetes still occurs, so it probably passes by the sympathetic chain.

Seeing that the "diabetic area" is close to the vagal area, it has been asserted that it is due to some vagal disturbance in the liver, but the division of splanchnics in which the vagus nerve impales does to the liver does not produce diabetes.

It has also been asserted that the spinal bulb acts as an inhibitory center in regard to the sugar-producing activity.
of the hepatic cells, the artificial diabetes is due to
the failure of this influence.
Again it has been found that
stimulation of the nerves
going to the liver, going to the
feta causes an increase of sugar
in the blood of the hepatic veins,
showing that stimulation of
these nerves in some way affects
the hepatic cells.
Sympharyngeal diabetes may also be
produced by the administration
of carbon disulphide, cyanide, carbon
monoxide, amyl nitrite, chloroform,
chloral, atropine, ouabain, and
other drugs. These drugs probably
act in the same way as the
fumetane into the bulb, they do
act on the central nervous
system as to cause a stimulus
to be transmitted to the liver
This stimulus causes the
pancreas to discharge its store
of glycogen.
Diabetes may also be induced by administering phloridzin, a glucoside derived from the bark of the root of apple trees; in this case, the sugar appears in the urine a few hours after and continues as long as the administration of phloridzin is kept up. This has also been given to the human subject with exactly the same result. It has been ascertained by experiments on animals that sugar was excreted even when the dog had been fasting so that no glycogen would be stored up in the body; this is one of the proofs of the production of carbohydrates from protein. The blood in this condition is said to be rich in grape sugar. The explanation given of this phenomenon of glycosuria is that the phloridzin acts upon
The renal epithelium ceases to destroy its power of keeping back the sugar & to cause it to escape upon the sugar held in solution in the blood. (Von Norden on Diabetes, "Twentieth Century Practice of Medicine Vol 1 P. 50). From this it has been assumed that diabetes mellitus is a disease of the kidneys, but there is not the slightest ground for this.

We now pass after these preliminary remarks to the pathology of diabetes mellitus: 2 chief theories are given viz.,
I. Over production of sugar.
II. Under consumption of sugar in the body.

Over production of sugar.
Under this head may be explained these conditions: where too much carbohydrates food is ingested where glycemia results from irritation in the}

...
of the nervous system, here the increase is due to a too rapid change of glycogen into glucose. The explanation given is that as a result of the new motor paralysis of the liver the hepatic artery dilates and an increased flow of blood through the liver takes place, one objection to this is that renal is probably caused by the portal vein not the hepatic artery as said above. The condition in these cases is only a temporary one. A broad ground of objection has been taken by Page (The Principle of Practice of Medicine Vol II p 532 3rd Edit) to this theory on the strength of the observation that in severe cases of diabetes kept on strict diet much more glycogen is formed by the urine than could be accounted for by
The ingestion of nectar, taken in the 24 hours by a diabetic patient.

In some cases of diabetes, the glycemia depends on the kind of carbohydrate ingested, for instance, grape-sugar raises the percentage of sugar in the urine to the highest point. Trehalose only raises it to half the extent while milk and cane sugar occupy a middle place. The theory of over-production of sugar is inexplicable on this point but this is easily applicable on the theory of diminished consumption. (Von Norden in "Diabetes Mellitus: Twentieth Century Practice of Medicine" Vol II P 82 1895.)

II The cause of an under-consumption of sugar: this may be due to:

1. Insufficient capacity of the glycogen reservoirs.

2. Insufficient consumption of
sugar in the tissue.

In sufficient capacity of the
glycogen reservoirs, i.e., that the
sugar is not daily put away in the liver and muscles.

The glycogen reservoirs may not
be capable of storing away
the carbohydrates which have
found access to the
circulation frequently.

There is more sugar in the body than
can be digested of by the
cells of the body; but, if the
liver be examined after death,
it does not show the diminution
in the amount of sugar which
we should expect again
though Bernard obtained
glycemia after ligation of
the portal vein, the same
result does not follow after
circumcision in man (Page "The
Principles and Practice of
Medicine" Vol 11. 1887 3rd Edit).

Moreover glycemia does not
intervene upon severe parenchymatous diseases of the liver or yellow atrophy of the liver, when the cells are destroyed and if it be due to a stage one would expect sugar in the urine when the reservoirs are destroyed in a maddled condition.

Besides, it is urged that the muscles, other glands act as glygen reservoirs, if this theory be correct then all the gycogen deposits must have become inefficient (Von Monder or Diabetes Mellitus "Twentieth Century Practice of Medicine" Vol II P 68).

Another objection to this is given by Fagee ("The Principles of Practice of Medicine" Vol II P 554 3rd Ed.) if a diabetic patient whose urine has been kept free from sugar by diet diet, e.a. come
Saccarine food, his urine becomes saccharine and continues so for some time afterwards, but the sugar in the urine is in far greater amount than could be accounted for by the amount injected. Now, Sage says, if we admit that the liver is the organ which supplies the blood with sugar, it must be the liver that this saccharine food acts injuriously on; here the supposition evidently is that the saccharine material must exert some influence on the hepatic cells as to cause them to form glycogen, restore it up in some time afterward, but, the saccharine material may not so much exert an influence on the liver cells as on the nervous mechanism thus causing the cells to form glycogen for
come time afterward.

2. Insufficient consumption of sugar in the tissues: here the sugar is deposited normally as glycogen in the liver but its further appropriation is interfered with, the sugar is not absorbed and discharged in the process of metabolism in the tissues.

This is supported by the investigations of Le& Harrist into the gaseous interchange during respiration (Von Marden on Diabetes Mellita, "Twentieth Century Practice of Medicine" Vol II, p.9 1895). It is known than an individual existing on a mixed diet gives out less CO₂ than he receives O₂ the ratio being on an average 9:10. This is expressed by the fraction 0.9, called the "respiratory quotient." This quotient becomes greater
when increased amount of carbohydrates are consumed in the body, it becomes smaller approaching 0.7 when a larger amount proportionally of albuminate fat is consumed. Now these authors found that in diabetics who were fasting the respiratory quotient was considerably depressed and that contrary to what is observed in healthy subjects it was not appreciably increased by the injection of carbohydrates. Chauveau and Kaufmann deny these experiments as they examined the blood of the carotid artery and vein in healthy and diabetic dogs to determine the amount of sugar. They found the difference in the amount of sugar between arterial venous blood was the same in both healthy
and cleared blood, and those experiments in the blood cannot be relied on (Von Norden, Diabetes Mellitus, "Twentieth Century Practice of Medicine" Vol II 16-9).

Against this theory of insufficient consumption we have the fact that if we had to do with a lower liver consuming power, then the glycogen storage reservoir would be filled to their utmost, but it is found that the livers of men and women invariably contain but little glycogen.

If deficient oxidation is the cause then we shall expect to find diabetes in cases of cyanosis, e.g. Koch's, emphysema, or cardiac disease but such is not the case. (Pappe, "The Principles and Practice of Medicine" Vol II B 83. 3rd Ed.)
Also in cases of phosphorus poisoning when oxidation is much interfered with, fluure is still split up ready for oxidation (Fawce, "The Temple Practice of Medicine" Vol. I., 883 Edit-3rd).

Again if diminished destruction were the cause then it is likely was storing its glycogen normally the diminished destruction of sugar in the tissue would keep the amount in the blood wine at a justly uniform quantity, but in diabece it is known that the sugar excreted by the kidneys is increased after each meal. This may defend though or the amount of carbo hydrate taken in with each meal. As in this case the carbohydrates may act injuriously on the nervous system cases as
It causes the liver cells to act more rapidly.
In both these cases it may be due to nervous influence a result of the absence of a ferment, perhaps furnished by the pancreas or the presence of toxic substances in the blood.

It has been said in the preceding pages that extirpation of the pancreas in dogs, cats, rabbits leads to diabetes, now the results of these experiments may shortly be stated as follows:

Only complete removal or destruction of pancreas is followed by all the symptoms, viz, polyphagia, polydipsia, polyuria and glycosuria.

All the animals rapidly lose flesh and suffer from great muscular weakness and generally die of coma without complications.
such as phlegmonous pneumonia.

2 Partial removal of gland a ligation of the pancreatic ducts is not followed by hyperosmocia not until atrophy of the gland has occurred.

But after complete ligation of all the blood, lymph vessels connected with the gland diabetes occurs. (V. Harley, in “Pathogenesis of Pancreatic Diabetes” Brit Med Jour Aug 27 1892. P. 433)

In 34 days de Dominicis removed the entire pancreas 4/13 of these never had any diabetes (Med. Hochenzel 1891 P. 717), but von Neurig, Minkowski, V. Harley and others found that if the pancreas is completely removed then only does diabetes follow, the former experimenter (Von Neurig) discovered that if a portion of the pancreas was left on attached to the abdominal
walk with its blood supply intact, diabetes does not occur.

(W. Hanley, "Pancreatic Diabetes in Animals and Man," Med Chron
icle Vol III 1895, 323).

Some experimenters have said that in the above experiments some nerve injury was the cause, this seems to prove the contrary.

The sugar in the blood of dogs operated on thymus, from 0.05 to 0.15% to 0.3 to 0.46%. We have now to see what is the cause of the sugar in the urine and the rapid wasting which follows.

Heyden suggests that the increased formation of sugar may be due to increased wasting of the tissue proteins, as there is always an increased nitrogen excretion and a loss of weight, but this theory is not supported.
Lépine & Banal (Lyon Med 1889 P619 & 1890 P53 P56) consider that it is due to the want of a ferment (the glycogenic, they have named it) which normally is formed by the pancreas and passed through the lymph stream into the general circulation to destroy the sugar. This is supported by the fact that the blood taken from the body possesses the power of destroying sugar.

V. Harley ("The Behaviour of Saccharine matter in the Blood" Jour of Physiol Vol XII 1891 P391) & Lépine state that the blood of diabetic dogs has not this power.

Lépine bases his opinion on the following experiment: he obtained blood from the vascular system half of which he heated to 84°C thus destroying the glycogenic...
ferment. He then put both samples of blood in an incubator at 39°C after an hour he examined both samples for sugar and found less sugar in the non-heated than in the heated, when the blood of healthy animals and men was used, but where the blood of animal where the pancreas had been removed and in men suffering from diabetes was used, he found little difference.

Several experiments have been made by men such as de Jong, Kraus,inkowski as they did not obtain similar results. Moreover we have seen before that experiments on blood taken from the body cannot be relied on as to the conditions existing in circulating blood. (Von Monden, Swiney Century Practice of Medicine)
The effects produced by the absence of pancreatic juice from the intestine have been studied by H. Darby (Tours of Path. Act., Vol. III, p. 245, 1895—"Absorption and Metabolism in the Function of the Pancreatic Duct"). If the feces are examined, they have an excessively foul odor; in them are seen large quantities of undigested food. Afrom experiment in dogs he found that after removal of the pancreas only 15–20% of foodstuffs was absorbed; 45 to 28% was absorbed and of carbohydrates 57 to 60% can be absorbed. But, as the animal gets weaker, less is absorbed (H. Darby, Tours of Physiol. Vol. XVIII, p. 1895—"The Normal Absorption of Fat and the Effect of Expiration of the
Pancreas, on it). Chemical analysis of the feces shows that instead of the normal 6 to 8% of nitrogen being excreted 20 to 50% is eliminated and in the case of fat 0 to 50% while in health only 2 to 6%. As the emaciation is probably due to defective absorption of proteins, fats and carbohydrates while the defective assimilation of sugar is also one of the factors. Mal-assimilation is supported by the fact that fatty degeneration of the liver muscles etc. takes place after removal of the pancreas in dogs. The cause of the wasting may also be due to an auto-intoxication arising from the substances normally secreted by the pancreas being retained in the body forming quiescences whose toxic effects lead to
Tissue waste.
This is supported by the fact that wasting occurs both in
juvenile of the pancreatic duct
in cases of partial
exstirpation & more over from
the fact that after experimental
diabetes in dogs sugar may
disappear from the urine but
still the wasting continues.
As a result of these experiments
we must take notice of the
important point viz. that
glycojen is not deposited in
the normal way in muscles &
liver after extirpation of the
pancreas fr in these depot
as a trace of glycojen is
observed while there is no
evidence to show that there is
a normally increased new
formation of sugar.
Ebnstein (Hoffmeister in Diabetes
"Clinical Lectures on Medicine &
Surgery by German Authors")
Lydenham Society, Third Series 1844 T.161) after the absence of the proto-plant having lost its power of producing as much CO₂ from an equal quantity of carbohydrates as in healthy persons. He says that the action of diastatic ferment is impeded by CO₂ and that in diabetes this being deficient, the carbohydrates, especially glycogen are insufficiently protected and are converted in large quantities into diffusible carbohydrates, particularly sugar which is thus excited by the urine.

Now, Lea (Central Bl. f. klin Med. July 25 1892) says if diminution of CO₂ is the cause of increased sugar production then an increased amount of CO₂ should diminish the quantity of sugar in the urine, he experimented thus:- 3 diabetes were made
to breathe an atmosphere in which CO₂ was increased (it has been found experimentally that in this way the amount of CO₂ in the tissues is also increased). He found that there was no diminution in the amount of sugar in the urine. It has been said that less CO₂ is found in the air expired by a diabetic, but this was not so in 5 cases experimented on by Less. He also found that the blood of diabetics shows a normal proportion of CO₂.

Pare (Physiology of the Carbohydrates 1847) says, "The disease essentially consists of a loss of sugar. A loss impairment of the power which normally dispose of ingested carbohydrate matter. It prevents its reaching the circulation in the form of free sugar." The deviation from the natural state depends in
The first place as regards degree upon the extent to which the impairment of the power of absorption exists in the next upon the amount of carbohydrate injected.

He says that the cells of the villi and of the liver are the agents by which the appropriation of carbohydrate is effected, but the fault does not lie with the protoplasm. The disease arises according to Payr from a lesion affecting a mechanism involving a loss of power in vasomotor centres with consequent direct paralysis of the muscular coats of the vessels. As a result of this vasomotor paralysis we get an unduly oxygenated condition of the blood such as would occur from the blood flow being increased through the capillaries and dearterialization.
not taking place. The oxygenated blood interferes with the formation of amyloid substance and allows the sugar to pass through the liver unaltered only facilitating the reversion of the amyloid substance into sugar. The evidence inclines to the belief that some kind of structural change stands at the foundation of diabetes.

Having mentioned the various theories given the evidence for and against each, we shall now see whether we can come to any definite conclusion as to the causation of the disease. Some authorities explain diabetes by describing various kinds such as hepatic, neurogenous, pancreatic etc. and say that the term diabetes is not a disease but a symptom. But such is probably not the
care for the disease varies greatly according to the individual especially as regards age and according to the extent to which the disease has advanced. If we turn to the recent experiments on the pancreas in animals we find that (a) total extirpation is followed immediately by all the symptoms of diabetes mellitus while (b) partial extirpation, tying off the pancreatic vessels, none of these produce diabetes mellitus but lead to cirrhosis of pancreas are followed by a goiter, polyuria, and vomiting.

Now, is this diabetes which follows upon complete extirpation a result of the removal of the pancreas or is it due to some lesion incidental to the operation? The latter is probably the correct explanation.
for if extirpation of the pancreas causes diabetes, we would expect ligation of the
pancreatic vessels to produce the same result, but such is
found not to be the case.

If we turn to the human subject we find that cases occur where all the sympathetic
ganglia were markedly diseased but yet the pancreas was quite
normal in a severe case of diabetes.

Again if we turn to the microscopical histology of the pancreas we find that cirrhotic changes
have frequently been described in diabetes. To this condition has
been attributed the cause of the disease. But this can be
settled. The changes in the pancreas in diseases other than
diabetes must be ascertained, for instance we find cirrhosis
of the pancreas in connection
with ophthalmitis, alcoholism and arteriosclerosis. The cirrhosis in the
pancreas may be a secondary condition due to the atrophic
change taking place in the organism. Moreover, the cirrhosis
in cases of diabetes is not constant and there is no
experimental evidence to show that cirrhosis of the pancreas
would give rise to it.

In cases of diffuse carcinoma of the pancreas where the organ
is completely destroyed, no sugar has been discovered in
the urine, this seems to negative the pancreatic origin of the
disease. It has been said

That (Med. Chronicle Vol III 1893
Aug. 9 823, "Pancreatic Diabetes
in Animals & Man") that the
carcinomatous cells may take on the function of the
pancreatic cells & form sugar.
But if this were so, we
should have the carcinomatous cells in cancer of the breast taking on the function of the breast cells forming milk.

As regards M. Sépinié, work on the glycolytic ferment of the blood. The objections to this theory are -

1. Pancreas in some cases of diabetes is quite healthy after death.

2. The evidence in the whole seems to favour an "overproduction" theory than that of diminished consumption.

3. All ferments are justly reduced in wasting diseases.

11. As we have seen under the head of pathology, the question whether the existence of this ferment is a vital phenomenon could not be considered settled. Accepting the existence of this ferment we should expect
In case of diabetes ascribed to disease of the pancreas, some improvement is seen by feeding the patient with raw pancreas or pancreatic extracts. If we turn to the disease Mæcædema, we find marked improvement has followed upon feeding the patient with thyroid extract when evidently the blood is deficient in some secretion or ferment manufactured normally by the thyroid gland.

In the case of feeding diabetics with pancreatic extracts as marked improvement has yet been recorded. This seems to be one of the most serious objections to the pancreatic theory of diabetes.

Recently De Raffi de Reale (Von Noorden on Diabetes Mellitus, Twentieth Century Practice of Medicine Vol II 182).
say that they have obtained
the same results from
exstirpation of the salivary
plands as also from entire
section of the duodenum, but
others have denied this.
Let us now turn to the
nervous system. In it appears
that some disease of this
system plays an important part
in the causation of the disease.
In cases of diabetes, it appears
to be due to some abnormal
activity of the liver cells
themselves, perhaps by the
direct action of the secretory
nerves upon them.
In all probability an
inhibitory center in the liver
exists in the medulla oblongata
next to the vasomotor center.
This exerts an influence on the
sugar-producing activity of the
hepatic cells, in cases of
disease or injury of the
nervous system this influence is destroyed and as a result of this we get diabetes.

This seems to be supported by the fact that in some cases of diseased injury to the nervous system a permanent diabetes is set up. Here we must suppose that the inhibitory influence is cut off and a permanent irritation proceeds directly. In reflexly under certain circumstances from the organically injured or functionally diseased portions of the nervous system it is transmitted to the liver cells. Here owing to the inhibitory influence being cut off are unable to accumulate the glycogen as in the normal condition.

It is known that a cardiac inhibitory centre exists in the medulla. From the fact that
The flow of saliva may be increased or diminished by mental emotions. It is evident that impressions from the auricles are capable of stimulating the centre to action or of inhibiting its action; now if an inhibitory centre exists in the heart and salivary glands is it not reasonable to suppose that one also exists for the liver? The area in case of diabetes in also partly increased and this seems to point to some abnormal activity of the liver cell. Diabetes has a certain predilection in individuals with a neuropathic stain, it also frequently follows upon neurasthenia showing that the nervous system appears to be connected in some way with it.
The effect of treatment seems to favour this theory, for opium is the only drug which is of any avail. We know that opium diminishes the secretion of the body and in the case of diabetics it probably acts by diminishing the activity of the secretory nerves to the liver and to a certain extent acts on the cells themselves. This inhibitory influence probably passes through the sympathetic chain and this may explain the cases of diabetes produced artificially, the coeliacplexus being probably injured. French says many acute nervous forms of diabetes go into chronic diabetes, in these individuals apparently a latent diabetic disposition awakened by nervous influence.
Under the heading it would be interesting to ascertain the condition of the sympathetic ganglia in a series of cases of diabetes.

Complications.
Under this head coma and anoxemia will only be referred to. In coma the following abnormal constituents have been found in the urine, viz., acetone, aceto-acetic acid, citoxic acid and butyric acid.

Pathology.
The coma has been attributed to fat emboli in the lungs as it has been found associated with hinaemia (Edin Med Jour. July 1879. p. 44) in the same journal in Sept 1882 a case of diabetic coma with hinaemia is recorded, here the fat was universally distributed throughout the
Blood was found adhering largely to the side of the blood vessels causing an obstruction to the flow and resulting in congestion and extravasation of vascular contents, but...

Cases are on record where the amount of fat has been exceedingly great but a most pernicious investigation of the lungs, kidneys discovered no emboli.

Amount of fat in the blood is not larger than usual.

Garveye Phycological Chemistry
Part II p.171

Sir Walter Peter V. Kausmaul
("The Theory & Practice of Medicine"
Robert 9th Edit 1885) attribute the diabetic coma to acetone from the fact that it is present in large quantities in the blood urine of diabetic patients and from the acetone-like odour of
The heart - but Dr. West (Franklin Vol. 2 1889 p. 137) found that this acetone was rare in healthy persons but common in persons suffering from acute septicemia diseases. Though common in diabetics with coma yet it may disappear when coma develops. Large doses of acetone may be given to rabbits without producing any marked physiological effect, but if any effect is produced the symptoms are not like coma! (Sampee "Physiological Chemistry" Vol 7 p. 167.) Again this acetone may be present for weeks or months then disappear without giving rise to coma.

the cause and suggestions as to treatment" has performed some experiments
on dogs with reference to coma. He injected grape sugar into the blood. Then he fed the animals. The dogs then passed into an irritable stage and finally passed into coma. By quantitative analysis, he found that lactic acid was increased in the blood after the injection. That it did not tend to fall as the sugar did, he also found in the urine after the lactic acid was oxidized, acetone, \(^{+}\)acetoylactic acid. During the irritable stage the \(CO_2\) absorbed and eliminated was increased but during the coma the reverse was the case. This points to great alteration in the metabolism. It has been found that hydrochloric acid produces similar results in rabbits, but if sodium carbonate be injected these symptoms are prevented.
on days with reference to coma. He injected grape sugar into the blood; then fed the animals. The dogs then passed into an irritable stage and finally passed into coma.

By quantitative analysis he found that lactic acid was increased in the blood after the injection and that it did not tend to fall as the sugar did, he also found in the urine after the lipase was burned, acetone and aceto-acetic acid.

During the irritable stage the CO₂ was increased and eliminated. It was increased but during the coma the reverse was the case. This point to great alteration in the metabolism. It has been found that hydrochloric acid produces similar results in rabbits, but if sodium carbonate be injected these symptoms are prevented.
Normally in the blood the CO₂ is supposed to be combined with the sodium carbonate and bicarbonate, and the hydrochloric acid is supposed to combine with the latter, rendering them unable to act as CO₂ carriers.

From the fact that acids in the blood were found that elimination of CO₂ was decreased. Halsey ascribes this coma as due to a diminished alkalinity of the blood produced by the acid products derived from the breakdown of sugar, the acids combining with sodium carbonate and bicarbonate and ammonia to be absorbed. This acidification in the organism is Finsler's...
destruction of albumen. In other diseases with great destruction of albumen coma occurs without the accumulation of acids in the organism.

As regards the formation of acetone and aceto-acetic acid they are supposed to be derived from the decomposition of the albumen of the body as they appear when the albumen of the body is being destroyed. Insufficient nourishment, starvation or poisoning by toxic substances, and acetoneuria often occur when the output of nitrogen is greater than the income.

The general opinion as regards diabetic coma seems to be that it is due to an "acid intoxication", Stadelman, Minkowski & Von Jaksch support this view. (Von Rooden in Diabetes Mellitus, "Twentieth
Century Practice of Medicine Vol 17 P. 98) and the acid which appears to give rise to it is butyric acid. This has been said to be the first stage in the formation of aceto-acetic acid, but butyric acid does not make its appearance in similar cases to aceto-acetic acid. It is often absent in some cases of marked wasting such as pulmonary, is absent from those in good physical condition. When butyric acid once appears in the urine of patient with diabetes it is permanent to show a constant tendency to increase and in most cases diabetic coma ensues. While engaged in practice in Durham in 1865, a diabetic patient presenting the complications of coma...
Jangrene came under my care; he was a sufferer of neurotic temperament; aged 72 years. He had been attended for three years previously by my principal D Ruther and he presented all the ordinary symptoms of diabetes mellitus, viz., parched condition of the mouth, thirst, constipation. The feces always being described to me as "hard every day". The urine contained an unusually large amount of sugar, the specific gravity being usually about 1050. Thin as in all diabetics was at all times dry. Mental instability formed a marked feature of the case. There were several attacks of hectic Mal. He also complained of somnolence and numbness of the left hand and also a persistent feeling of coldness.
of the thumb & fingers, power remained unaffected, the anaesthesia extended slowly so that at the end of some weeks the pricklings & sense of coldness affected the skin of the far arm, these symptoms I regarded as a peripheral neuritis. In December 1875 a small patch of gangrene appeared in the sole of the right foot & while suffering from this condition he developed on three different occasions symptoms of "threaening coma" viz, marked emaciation, pain in the epigastrium, dry dry tongue, faint thirst, decrease in the pulse of the heart. He was very drowsy & if spoken to, would turn round and answer but immediately would drop off into the drowsy condition again. Now, though he
Presented exactly the same symptoms in three different pecansm, the coma was waved off by the administration of alkalies, acting frupatines, viz., Jalap & Calomel. It appears as if the coma is due to the formation of some noxious substance in the alimentary canal. During the attacks there was always a reduced secretion of sugar, and this seems to point to the sugar being broken up into some poisonous substance before it reaches the general circulation. In experimental pancreatic diabetes, it is found before the recurrence of coma that sugar disappears from the blood & Hailey (Brit Med Jour Sept 23/93, P667. "Diabetic Coma its Etiology & Suggestions as to Treatment") explains this phenomenon has probably
presented exactly the same symptoms in three different occasions, the coma was
waxed off by the administration of alkalies, yielding purgatives, viz., Jalapi & Calomel. It
appears as if the coma is due to the formation of some toxic substance in the
 alimentary canal. During the attack there was always a
reduced secretion of sugar, and
this seems to point to the sugar being broken up into some poisonous substance before it
reaches the general circulation.
In experimental pancreatic diabetes, it is found before the
occurrence of coma that sugar
disappears from the blood of
Harley (Brit Med Jour Sept 23/93
p 667. "Diabetic Coma its
etiology & suggestions as to
treatment").). Thus it is
that the organism has probably
regained the power of breaking down the sugar molecule in the process of metabolism. Since the quantity present in the tissues and blood had been previously increased an excess of it produced increased glucose which caused the coma. In all probability the same products are being constantly formed in the human subject but they are either formed in such small quantities that they are rapidly eliminated, or else there is sufficient time for them to be further transformed in the process of metabolism into harmless substances.

Gangrene—
The same patient while I was attending him was attacked with gangrene on two different occasions. Before the case came under my care
my principal had also attended him for the same complication on the great toe or on the sole of the foot. In the first attack the slough had separated and the ulcer completely healed. In the second attack the slough separated and the ulcer never healed. He remained in this condition for about a year and during my attendance that he developed his third attack of gangrene. The disease commenced with a blob about the size of an ordinary bean on the under surface of the foot, it contained fluid which speedily became turbid. It was surrounded by a dusky purple areola. A distinct line of demarcation formed and the slough separated nicely. About a month after this attack a fourth patch of gangrene
gangrene appeared on the inner side of the foot commenced in exactly the same manner as the others had done.

The again a distinct line of demarcation formed and the plough showed every appearance of separating the last patch was considerably larger than the others being about 6 inches in length and 2 inches in breadth. It was just about the time that I left Durham and I was unable to follow the case further. As regards the pathology of diabetic gangrene Graves ("A Manual of Therapeutic Surgery" Vol 1 1841 p1614) gives it as due to endarteritis. This is explained by the fact of oxygen a its predecessor chemical substance circulating in the blood and causing irritation of the lining membrane of the vessels. It is also said
to be due to the innervation of
the part being interfered with
as a result of central
nervous disturbance.
From its chronic course in
this patient, its situation
from the fact that he
suffered from peripheral
neuritis of the upper extremity
on the same side, the disease
in all probability was of a
neurous origin. Moreover there
was no thickening of the
arterial vessels to be made
out. This case was very
interesting from the fact
that the gangrene broke out
on four different occasions,
but yet there was no tendency
to spread as is usually the
case, the course of the
disease in diabetic being
generally very rapid.
As regards the treatment of
these two complications: in
The time for treatment is during the "threatening stage"; when coma is once established we are powerless.

Stadelman recommends the administration of a saturated solution of alkali, viz. 4 drams of soda bicarb + 2 drams of citric acid dissolved in 8 ounces of water & flavoured with a little saccharine essence of lemon. This should be taken twice a day, & if necessary, twice daily. (A Manual of Medical Treatment in Clinical Therapeutics, G. B. Burney, 1884, Vol. II, 4th Ed.)

Intravenous injections of alkaline or saline fluids have been tried but no marked success has yet been recorded. Large doses of alkali or the administration of injurious poisons are the best treatment to adopt.
In gangrene alkalies with a little bromide of potassium are again of service and locally the application of antiseptic remedies. In this case charcoal poultices were used till the line of demarcation formed, then a carbolic acid lotion was applied. As regards amputation if the disease shows no tendency to spread it is best left to nature, but if rapidly spreading amputation would give the patient the best chance.

Treatment of diabetes mellitus:
When we take into consideration the different nature of every individual, inherited disposition, conditions of life etc., we can easily understand why it is best that no routine treatment should be adopted but that each case should be
treated in strict accordance
with the form of diabetes
it presents. We shall divide
the treatment into -

I Hygienic
II Dietetic
III Medicinal
IV Hygienic:

Special attention must be
paid to the room, well-ventilated,
keeping the bedrooms are
desirable. Muscular exercise
should be insisted on, that
of fatigue, he should never
be over-tired for this often
being in the fatal coma, a
special attention should be
paid to this if there is any
Degenerative change in the heart.
when such is the case riding,
driving and gardening may
be resorted to. The amount of
sugar in the urine will be a
good guide to the amount
of exercise which can be performed.
Special attention must also be paid to the teeth, chin and bowels. There is a great tendency to caries of the teeth owing to the acid secretion of the buccal cavity, which may be best prevented by careful attention to cleansing.

In account of the dryness of the chin, baths should be taken 2 or 3 times a week; where the condition is robust, cold baths, or douches should be used, but where there is any tendency to cold hands and feet then lukewarm baths are preferable. It is very important to combat the tendency to constipation as this condition predisposes to coma; it is best met by some of the alkaline sulphur water, a little jalap and cascara.

We should be urged to continue
his occupation as long as possible but should have a
change of air at least once a year, a simple pleasure
like a visit to some health
want.

II. Dietetics:
Here the chief aim must be
to restrict and if necessary
cut off altogether the supply
of carbohydrates from the food.
This is especially important in
the acute forms of the disease
which occurs generally in young
subjects, while in older persons
where the disease runs a
chronic course the total
restriction does not seem so
important. It has been found
that in individuals who have
been kept for several weeks
on a diet containing no
starchy food often acquire a tolerance for
carbohydrates excessive much.
less sugar after the ingestion of a certain quantity of amylaceous food than they did before. Saccharine must be used instead of sugar.

Bread is the great difficulty, as none of its substitutes seem to satisfy the craving of the system. In this article of diet and patience, in course of time give them up, partly owing to their high price and still more on account of their indigestibility. The best plan seems to be to gradually withdraw the bread, if, under this regimen the sugar gradually disappears, some time may be allowed to elapse, then the bread be given again. We shall then be able to determine whether a tolerance for carbohydrates has been acquired, if so, small quantities of carbohydrates...
may be taken daily, but if sugar again appears in the urine then head must be forbidden altogether. Other cereals, rye, oats, barley etc. are just as harmful as head and peas, beans, lentils, arrowroot, tapioca, soy, rice, and potatoes must also be struck out of the dietary. All the vegetables, carrots, horseradish, garlic, onions and celery. The following vegetables may be allowed green cabbage, lettuce, French beans, spinach, watercress, radishes and the following in moderation, cauliflower, turnips, mushrooms, artichokes, raddish and cucumbers. All fruits such as pears, melons etc. must be forbidden. All fish, preserved meats & meats of all kind, eggs etc. may be allowed.
As regards beverages milk is generally interdicted, but in the cases that have come under my care milk was generally ordered and it did not increase the sugar in the urine to any great extent; the amount should be limited to about 2 pints per diem. Cream, butter, corn milk, rhumias may also be given, also tea & coffee in moderation.

Alcohol should be allowed in older persons but not in young of wine, a little Claret or Burgundy may be allowed. As regards fat Von Drosten in his book on Diabetes, Mellitus, Twentieth Century Practice of Medicine (1939) advocates its use. He says "the supplementing of a strictly flesh diet with fat marks an essential advance in
therapy of diabetes is greatly advocated by Carlsbad physicians who find that it agrees well with diabetics; it induces satiety much more quickly than meat. About 2/3 of a day should be allowed a better but the patient regulate the amount.

Medicinal

Opium or its alkaloids Morphia & Caidea with alkaline waters such as Carlsbad, Vichy & Vals is the line of treatment found most serviceable and has to be varied in detail from time to time in the same way as the dietary scheme according to the varying phases of the disorder. Whatever line of treatment is adopted, at the same time being the two points we have carefully to watch are the amount of sugar in the urine.
on the one hand and the amount of bodily vigor on the other. Whatever diminishes the one and adds to the other, whether it be restriction or relaxation of diet is succeeding ought to be persevered with.