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On the Hepatine of the Liver, & Its Relations to the Pathology of Diabetes Mellitus.

for Dr Laycock

It has been so universally recognised, as almost to have become a truism, that the advances which have been made in our knowledge of disease are for the most part dependent upon, or at least coincident with the gigantic strides which chemistry, physiology, & histology have taken within the last quarter of a century. In no case is this perhaps more evident than in that of those recent & brilliant discoveries which have been made by many of the most eminent physiologists of our day, & which throw light on a disease, whose nature & causes have baffled the ingenuity of medical men, during the two centuries which have passed since it was first distinctly recognised.

Before proceeding then to a short sketch of the pathology of Diabetes mellitus, - the disease I refer to - it will be well to review what have been justly termed the advances made in our knowledge of saccharine physiology of late years, more particularly with reference to the experiments & discoveries of the distinguished French & English physiologists, - M. Claude Bernard & Dr Pavy -

* I am merely stating at present the old theory

By the researches of various physiologists it has been satisfactorily determined, that the farinaceous & saccharine constituents of our food undergo certain chemical changes before being absorbed; — the starch being chiefly converted into dextrine & grape sugar, whilst the sugar is partly decomposed into lactic & butyric acids. After absorption, — which may be effected either by the lacteals, or by simple endosmose into the vessels; — decomposition into lactic & ultimately into CO_2 takes place, & thus these compounds by a process of oxidation help to keep up the heat of the animal body*. Sugar has never indeed till lately been discovered to be a constant ingredient of the blood, partly no doubt owing to its small quantity, & probably also to a great extent to defective chemical analysis. But that it is a normal constituent of the blood taken from all parts of the system, & which up to a recent time has been included among the extractiform matters, has been satisfactorily shown by the analyses of Daoy, Harley & others, & not only of the blood but it would seem, (tho' indeed in most minute quantities,) of the urine also, as maintained first by Brücke, & corroborated lately by Dr. Bence Jones.

That this sugar is in great part derived from the food is abundantly proved by the simple fact of its great increase after eating largely of saccharine or amylaceous articles, as shown by Von Beeker who found that, while the blood of rabbits fed on carrots contained as much as 0.584 p. cent sugar, that of rabbits fed on oats only yielded 0.109 p. cent, & after 24 hours starvation this was reduced to 0.045 p. cent. But whilst the saccharine & amylaceous constituents of the food are undoubtedly the principal sources of this sugar, it has been satisfactorily proved to have other origins. It was the observation of the fact, that sugar continued to be formed by Diabetics even tho' confined to a strictly animal diet, that led to the well known series of experiments by the illustrious physiologist Bernard, the brilliant results of which not only show his great talent in executing them, & the ingenuity he displayed in their interpretation, but led to the establishment of what is well known as the theory of the glycogenic function of the liver.—

It was in the year 1848 then that Bernard, while examining the constitution of the blood, found to his no small surprise, that tho' the blood of

the Portal vein & that of the system generally, in animals fed exclusively on animal substances, was destitute of sugar, that of the Hepatic vein, Inf. Cava, & Right side of the heart contained it in abundance. Finding too that the hepatic tissue alone after death gave evidence of sugar, he drew the immediate inference that the liver possessed a sugar forming function, that it threw the sugar into the blood, there to undergo oxidation & administer to the heat of the animal body. Such at least was the theory formed by Bernard at first, but like most other great theories it was destined to undergo important modifications, & not the least of those from the hands of the originator. He at first held the opinion that the liver possessed the power of forming this sugar out of the azotized or unazotized components of the Portal blood, & clearly demonstrated the fact, that after death, (— his experiments being all on blood post mortem, —) the blood between the liver & the lungs contained sugar independent of the nature of the aliment, or of the processes of digestion.

We need not go into the experiments by which he proved this. They have been repeated & corroborated so often that it would be superfluous to do more than state the fact. But the question

which at once struck him, whence was this sugar derived? Not necessarily from the aliment, as it is so abundant in the blood of carnivora as herbivora, & his experiments showed that it might be found in the hepatic blood of animals which had been killed whilst fasting. & Valentines observations in hybernating animals corroborated this fact. To elucidate this subject then he performed some experiments of the following nature —;

I. A dog was killed 4 hours after a full meal of meat & bones, & the abdomen at once opened. On examination of the chyle & chyme no sugar was found, but a large quantity in the trunks of the portal blood, & a less amount in that of the right chambers of the heart.

II. A dog was killed after fasting 3 days. There was nothing in stomach & intestines. No sugar in the chyle, but distinct evidence of it in the blood of the portal vein & right side of the heart.

The presence of sugar in the portal blood in both these experiments seems to have perplexed Bernard not a little, but his ingenious mind soon found a solution of the difficulty. He believed that one great cause of the portal circulation was the contraction of the abdominal parietes going on

during life, & that consequently as soon as the animal ceased to breathe this pressure would be taken off the circulation, & the result would be a reflux of blood from the liver into the portal vein. That this idea was correct he showed by the following experiment.

A dog while actively digesting animal food was killed by section of the medulla. The abdomen was at once opened, & ligatures placed on the splenic, pancreatic & portal veins just at its entrance into the liver. The blood was collected & examined, & no evidence of sugar could be found in the various branches of the portal vein, but when an opening was made in it on the hepatic side of the ligature, the blood that flowed out was collected & found to contain sugar.

Altho' these experiments proved that the production of sugar was independent of the elements of the food, yet they could scarcely be said to have given him a much greater insight into its true origin, but another of his experiments seemed to him to clear up what was still obscure.

Having fed a dog exclusively on meat for some days he killed it suddenly, opened its abdomen & removed the ~~ligature~~ liver before the blood could possibly have had time to coagulate. He then thoroughly washed out its tissue by injecting cold HO thro' the portal vein,

* Bis glycogen or hepatine when extracts from the hepatic cells by boiling, & precipitated by alcohol, is a white, tasteless, amorphous mass, soluble in HO, & has the chemical formula $C_{12} H_{12} O_{12}$

Continuing to do so, till the liver was exsanguine, & the issuing
H0 contained no trace of sugar, & till none could be got from
the liver tissue cut up & boiled. Having thus deprived it
of all saccharine matter he left it for 24 hours,
& then on examination found a large quantity of soluble
sugar, which must have been formed subsequently to
the injection of the H0, out of some previously insoluble
non-saccharine material. This showed him that the
sugar was not directly formed by the liver itself, &
that its formation was outside the vessels, & led to
his discovery, coincidently with Hensen & Pavy, of a
substance which having properties intermediate between
those of dextrine & hydrated starch, & being con-
vertible into sugar in the presence of any ferment,
he named *glycogen, but to which Pavy afterwards
gave the name of Hepatine or the Amyloid substance
of the liver. Bernard then finding that this sub-
stance was so easily convertible into sugar, &
that this process went on very actively after death,
was of course obliged to abandon the idea of the
vital action in the liver itself, & explain the
phenomena in some other way. He therefore came
to the conclusion that the glycogen was formed out
of the solid tissue of the liver itself by a
process of secretion, the secreting organs in this case
being

* May more, Bernard inquires that there may be a function of cells for the secretion of this substance & of the bile. He points out that this function of secretion is different from the usual ones, in being internal as to the blood, & not requiring an excretory duct. Is there any true relation, he asks, between the two secretions? Can we admit that the albuminous matters of the blood on arriving at the hepatic cells undergo disintegration, - the azotised portion serving for the production of bile, the hydrocarbonaceous for that of sugar? If so, the two secretions would go on at the same time, but experiment seems to prove that they rather alternate with one another, & that the secretion of the one seems to be at a minimum while that of the other is greatest. If we make a biliary fistula we find that the bile is secreted in greatest quantity 3-4 hours after a meal, while sugar is most abundant in from 3-4 hours, or while digestion is most active. But comparative physiology seems to give even stronger evidence. - In the Rhinoceros fleva we observe that, while intestinal ~~digestion~~ absorption is going on a saccharine liquid flows thro' the bile duct into the stomach, & continues to do so till it fills both the stomach & bile duct itself, giving rise to a considerable enlargement of the liver. This

*being the hepatic cells, in which it is here the glycogenic substance can be easily seen under the microscope.

Whenever this glycogen escaped from the cells into the blood, the immediate result was the production of sugar, which he had shown to be so constant an ingredient of the blood between the liver & the lungs, & indeed in such a proportion that the further from the liver we go the less sugar will be found.

Bernard's own view as to the use of the sugar in the animal economy evidently coincided, (at least at that time,) with those of the eminent chemist Liebig. He supposed that after leaving the liver it was gradually decomposed into lactic acid & HO & finally into CO_2 to be given off by the lungs, & thus serve in part to keep up the heat of the animal body. I believe that it is still an accepted theory with many physiologists that some part of the sugar in the blood may undergo such a decomposition. If so, it must be a very small quantity indeed, considering the minute quantity of sugar normally in the blood & that in the urine.

According to Bernard's idea at that time, the lungs & liver performed functions opposed to one another in the animal economy, the former destroying that

liquid thus is gradually absorbed from the stomach, just as this absorption is about at an end, a fluid bile flows thro' the same duct into the stomach. It is detained there apparently until the next meal. In the articulata there are evidently distinct anatomical arrangements for the third function, that for the sugar consisting of cells analogous to those of the liver in Vertebrata, & situated in the coats of the intestine.

* We are speaking of the time when sugar was supposed to be directly formed in the liver.

element in the blood produced by the latter.

But Bernard's theories as to the origin & destination of the sugar of liver were by no means left unattacked. Lehmann had from the very commencement of his experiments pointed out that the albuminous constituents of the food as well as the azotized product of the disintegration of the tissues, might by a process of decomposition be converted into sugar, — & a similar idea seems to be held by Groupe Besanez, who thought it fully corroborated by the fact discovered by Lehmann, that a smaller amount of albuminates existed in hepatic than portal blood.* That the amyloid substance may, in some way, be formed from the nitrogenous tissues & elements of the food, seems pretty evident from the fact of its formation going on even in a purely animal diet, as McDonnell has shown that amyloid cannot be extracted from the meat upon which these animals are fed. Nay, its formation also goes on even in the last stages of inanition. There cannot be the slightest doubt however that the really great source of the amyloid are the saccharine & farinaceous constituents of the food, & Bernard himself has shown that the amyloid obtained from the muscular tissue of a fasting horse was restored by a full meal. In fact the very much larger proportion of sugar discoverable after death in the liver

* This theory too is rejected by the fact of Degen being found in the liver of a foetus even as early as the 5th month, & in every order in the animal Kingdom, from as the Articulata & Mollusca. That the Degen in the liver of the foetus is not derived directly from the mother is proved by the fact that it is not to be found in the liver earlier than the 4th month. I have not the slightest doubt that the liver of animals fed for as long a time as is compatible with life on Leuchaus-farinaceous diet alone would be found to contain abundance of Degen after death.

I may here mention another wild theory put forward as to the origin of the amyloid, that it is the result of changes undergone by fatty matter normally taken in food, or generated from them in the liver itself. (Von Ritke seizing on the latter as the correct notion, has put forward a theory as to it being derived from the decomposition of the conjugated acid of the bile re-absorbed from the intestine. Both views appear to me highly improbable & have scarcely a shadow of evidence in their favour.

sion of herbivorous animals led to the idea that this was derived from the aliment direct, & simply stood up there. Hence Sawson published a paper in support of the old theory that the only real starch formers were vegetables.* That a part of this starch went to the growth & maintenance of its own tissues, whilst another part was stored up in cells ready to nourish such herbivorous animals as fed on it. By these in turn the starch is partly used up in the vital forces, & partly deposited in their tissues & more particularly in the liver, & it is to this latter source alone that he would trace all the sugar found in the blood of carnivora, a supposition which of course appears not only untenable but almost absurd when we know that it is still to be found in the liver after prolonged fasting, & even after animals have lain dormant for months.

Bernards original idea, it will be remembered, was, that the amyloid in some way was formed out of the gland tissues itself. He did not think that the sugar was directly deposited from the portal blood, but rather imagined that this went to form the fat which may be found so abundantly in most livers, or at least, that in herbivorous animals a portion of the saccharine constituents of the portal blood

* That fat may be formed from compounds of the saccharine group does not I think admit of doubt. Hence the fat in the livers of those unfortunate geese fed upon to obtain the famous foie gras. The formation of wax a true fat from honey by bees is another example. Both of these instances that starch & sugar in some way, (probably indirectly as we will afterwards see that the formation of amyloid, —) may contribute to the formation of fat.

pent for this purpose. He even went so far as to state that the production of fat was vicarious with that of sugar, the production of the former ceasing, if that of the latter be unusually large owing to puncture of the medulla: while fat is deficient in the liver of diabetics, sugar is deficient in fatty liver*. But that the liver possesses the power of transforming sugar into fat is by no means satisfactorily proved; the purpose to which sugar is applied in that organ being, as we shall see, probably very different. But not only have Bernard's theories as to the origin of amyloid tumours to, but it has also been satisfactorily proved by Rouveau, Harley, Pavy & others, that, far from ministering as a pabulum to keep up the animal heat, by a constant process of oxidation going on in the lungs, the amount of sugar found in the left side of the heart cannot be discovered to have undergone any appreciable diminution. Harley also in fact agrees with Griesinger that the sugar to a certain extent disappears in the capillaries of the system generally, for he found somewhat less in the vein than in the corresponding artery of a limb. He goes so far as to think that it must furnish directly to the various tissues & organs, some substance necessary either for their development, or the repair of what they have lost. If so I think that it must be evident that it

* Bernard was indeed led to abandon the oxidation theory himself at a later period, by finding sugar in the urinary bladder of foetuses at a very early age, & also by noticing that sugar passed thro' blood containing sugar had no more effect in destroying it than had CO_2, H, etc. The theory which he then formed as to its uses is rather a strange one. He many found that a substance capable of giving rise to sugar existed in the lungs & muscles of the foetus. He imagined that two kinds of fermentation took place there, - the one a conversion of this pre-existing azotised substance, (for so he imagined it to be,) into sugar, the other a lactic acid fermentation at the expense of the sugar. The first alone he thought went on in natural intra-uterine life, & the sugar is connected, he thinks, with the development of the tissues, ceasing to be formed altogether however from the 8th or 9th months. Accordingly, attempting to apply this theory to the adult, he states that the most important uses of the sugar are fulfilled in the liver at the moment when the albuminous materials are being disintegrated to give rise to the

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cannot be in the form of sugar that it is subservient to the nutrition, for tho' a form of sugar termed "inosite" has been discovered in muscle, yet it would seem certainly to be the product of the desintegration of albuminous substances. He Pavy altogether denies that sugar can undergo direct oxidation in the animal body, he believes, that from whatever source it may be derived, it will be excreted by the kidneys: for he knows of no process by which its destruction could be effected in any part of the circulatory system. This statement at last coincides with his own experiments as to the small quantity of sugar normally in the blood, & with those of Bricke & Bence Jones as to its constant presence in the urine. Like a great many other theories which have not stood the test of time, that of Liebig as to the destruction of sugar in the lungs, was accepted as true without any great evidence in its favour, strongly corroborated as it appeared to be by the glycogenic theory, & the preconceived views of its supporters. Hence when the one theory was proved fallacious, the other necessarily fell with it.

Before proceeding to consider Pavy's discoveries, we must shortly allude to the experiments which Bernard performed, to elucidate the influence of the nervous system upon the glycogenic function. Like all other functions of the animal body he naturally imagined that it

must

sugar, for it is precisely at this moment that those organic
elements are formed, which ultimately accomplish this
evolution, either to form new tissues, or assist in the nu-
trition of the old.

must in some way be under the control of the nervous system, & it was in prosecuting researches to this end that he accidentally discovered, that, by pricking a part of the floor of the 4th Ventricle near the origin of the Pneumogastric Nerve, a temporary artificial Diabetes was created, the duration of which never exceeded a few days. So rapid indeed is the production of sugar in such a case, that it can according to the discoverer himself, be found in every secretion except the saliva in twenty minutes after the operation. But if the irritation be too great, or a powerful galvanic shock transmitted thro' the part, its production will soon cease. A similar explanation has been given of the fact, that sugar is so seldom found in the human liver after death; all nervous energy it is supposed being exhausted by the disease which carries the patient off. Even in the last stages of Diabetes sugar ceases to appear. Bernard's idea was at first that the stimulus was simply conveyed by the Pneumogastrics to the liver to control the glycogenic function, but he was soon obliged to abandon this simple explanation, for he found that other nerve lesions produced a similar result, as e.g. irritation of the olivary bodies even after section of the vagi. Having found too that the inhalation of $C_2 HCl_3$ & other irritating vapours sufficed to give rise to glycosuria, he formed the theory, so long generally accepted, that the normal stimulus, originating from

the action of the air on the terminal branches of the pneumo gastrics in the lungs, was conveyed by them to the medulla, & thence propagated to the liver thro' the spinal cord & great sympathetic; being thus a great reflex action with the medulla as its centre. This theory derived its chief support from the fact that division of the cervical vagi arrests the secretion of sugar, & because while irritation of the lower part of the cut nerve produced no result, a temporary Diabetes is excited by pinching the upper. If the cord be divided too below the origin of the phrenic nerves, (or as low as we can divide it & preserve life,) irritation of the vagi has no effect in producing diabetes.

This theory like the others promulgated by its discoverer was by no means left in its integrity. Hurley was the first to differ from the views of the eminent French physiologists. Regarding a saccharine state of the urine very justly as only a symptom of a disease, he points out that the sugar might arise in different ways. There might be some impediment to its assimilation, & then of course accumulating in the blood, the surplus would necessarily escape by the urine. Or it might originate in some change in the secreting organ itself producing a more than usual activity in the discharge of its function, or by an artificial irritation of the nerves, as by breathing irritating vapours. He objects however ingeniously to Bernard's idea that the normal stimulus was sup-

* Due probably in the first case to the more rapid flow of the
thro' the lungs, & the non assimilation in consequence of a part
of the poisonous elements.

§ The prolonged use of alcohol has been mentioned as one
of the causes of Diabetes mellitus.

plied by the air in the lungs. If such were the case, we would expect to find little variation in the amount of sugar throughout the day. Such however is not the case. The production of sugar varies greatly, being at one time nearly dormant, at another very active, without any corresponding change in the respiratory process. We therefore believe that we will find the real origin of the stimulus in the organ itself, & probably in the stimulating effect exerted by the portal blood on the hepatic branches of the vagi. His experiments in support of this view, consisted in the injection into the portal circulation of substances, which we may justly consider irritating, such as ether, C_2H_6O & the ligor ammonia. These invariably produced artificial Diabetes. On like manner he explains the effect of the food in producing sugar in the urine, - the portal blood being then necessarily most stimulating*. The absence of this stimulus would explain the fact, he thinks, that the production of sugar falls to a minimum in a fasting animal, or one fed only on fatty matters which being taken up solely by the lacteals can add nothing to the stimulating quality of the portal blood. In the same way bad glycosuria may result from the injection of ether etc into the duodenum§, & an experiment conducted on himself corroborates his theory, - viz, that having eaten largely of a highly spiced asparagus salad he became diabetic

* A slow lingering death generally causes the disappearance of sugar from the liver.

§ We may here mention some of the theories brought forward in opposition to that of Bernard. Amongst others Seguin, reviving an old idea of Mialhe's, thought it more natural to consider the liver as an excreting organ like the kidneys, than as one capable of performing the important function attributed to it. He imagined that it might simply separate from the blood, lay up in its tissue the sugar passing through it, & would restore it little by little to the blood. As M. Seguin admitted the fact of the liver containing sugar (after death) independent if the ferment, all that was necessary to disprove his theory was to show that hepatic blood did not contain sugar in appreciable quantity after prolonged fasting, while it might reappear again on an animal's diet solely. This was easily done, &

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& continued so to his no small alarm, for several days.
One strong argument against his theory, he disposed of rather ingeniously, viz the fact already mentioned, that division of the cervical vagi arrests the production of sugar, but not so section of the same nerves below the lungs. But the liver ceases to secrete sugar in cases of very severe operations, if a febrile state be induced, & the fact that the serious attack of some other disease often arrests the discharge of sugar in Diabetes is strongly confirmatory of his view. The slow asphyxia* produced by section of the cervical vagi is, in itself, sufficient explanation of the disappearance of sugar from the liver, while the less severe nature of the other operation, (section of vagi below lungs,) neither producing any serious consequence at the time, nor producing death by asphyxia, readily explains why the production of sugar is not checked, & at the utmost only slightly disturbed by it. §

——— But the fundamental facts of Bernard's theory, have never been subjected to any very severe attack until very recently, when Dr Pavy published, in Guy's Hospital reports, papers to prove that, so far from the liver possessing a glycogenic function, the production of sugar is not a physiological process, but merely a chemical transformation, only taking place after death, & under certain morbid conditions of the system — & as his experiments have been conducted very carefully,

&

o. they do easily refute simply owed to strengthen the
fact brought forward by Bernard.

& the deductions derived from them appear to me very conclusive, & may be pardoned if I enter into them in some detail. It is not the correctness of Bernard's facts that Pavy impeaches, but the deductions derived from those facts, or rather the application of what may be termed pathological data to the explanation of a vital process. Pavy along with Hensen it will be remembered discovered that substance, to which Bernard about the same time gave the name of glycogen, but which Pavy objecting to that term as implying a theory in which he did not concur, called "Hepatine" or the "Amyloid Substance." Pavy however like most other physiologists had not only thoroughly believed in, but had even confirmed Bernard's theory. His experiments he had often repeated, & believed in fact that the production of sugar was, as much, if not more, a function of the liver, as that of bile, & his first experiments were simply to ascertain what was the influence of any particular diet on the production of Hepatic glycogen. His careful experiments & analyses did much to elucidate the subject, & he found —— that,

I. Average of analyses of Livers of dogs fed exclusively on animal diet — the dogs being killed suddenly & the livers at once removed — that gave

(a) Relative weight of liver substance to that of body — $\frac{3}{2}$ to $\frac{16}{1}$.

(b) Average proportion of amyloid in the liver — 4.19 p. cent.

II. Under a vegetable Diet — (a) Rel. wght of liver to body $\frac{3}{1}$ to $\frac{16}{1}$.

II)
(b.) Average proportion of amyloid 17.33 p. cent.

III. Under animal diet with sugar -

(a.) Rel. Wght of liver to body (nearly) 3 to 1 lb.

(b.) Average of amyloid - 14.5 p. cent.

These facts, which he satisfied himself of again & again, showed him most conclusively that the starch & sugar contained in the aliment were used by the liver in the production of the amyloid, & it was this fact which led him first of all to think it strange that the sugar should only be converted into amyloid to be transformed into sugar again. It was in fact while conducting some experiments as to the changes which the sugar, which he believed were still normally flowing from the liver, underwent in the lungs, that, having catheterised the right side of the heart of a living rabbit, he found, to his no little surprise, that he could scarcely get any of the characteristic sugar reaction, he had been so accustomed to from the blood of the same parts after death. This aroused his suspicion, & he repeated his experiments, taking every precaution that experience could direct.

That his analyses were conducted with the greatest care, & a desire to be impartial, will be evident from the fact that the amount of sugar he discovered in the right ventricular blood, he determined in 3 cases to be as little as the $\frac{47}{1000}$ lb., the $\frac{28}{1000}$ lb. & the $\frac{93}{1000}$ lb. of a grain p. cent. & we may in reality look upon the last as the nearest to the normal

we reflect for a moment on the fact which Harley had previously shown, that sugar is to be found in every vein corresponding to an artery throughout the body in quantities, any differences in which could scarcely admit of detection, it must be evident, (even granting that any amount of sugar was poured from the liver into the blood,) that, if such sugar escaped destruction to any appreciable extent in the lungs or in the capillary system generally, it ought as naturally to have been found in the vena portae as in the inf. vena cava. Indeed it seems strange to me that this should not have struck Harley himself. The discovery of sugar in the blood in those quantities proved at least that the liver was not throwing out sugar into the circulation in the large amount that Bernard imagined, & dealt a blow at the glycogenic theory in another way viz by disproving the fact so much relied on by its supporters that the blood of the hepatic vein & right side of heart differed in its composition from that in the system, & more particularly in the vena portae in animals fed solely on azotised diet.

Notts Parry had now distinctly disproved the passage of any material quantity of sugar into the blood during life, yet he was by no means still inclined to deny the glycogenic function of the liver, & he therefore proceeded

to discover
as nearly as possible the normal condition of that organ.
He had known for some time that the presence of an alkali
prevented the amyloid passing by the fermentative process
into sugar, & determined to try its effects on the liver itself.
He accordingly injected a pretty strong alkaline solution & found
on examination of the liver after death, that no sugar, or at the
most a mere trace was detectable in it by the most
delicate reactions, & that this was not owing to the
destruction of sugar by the alkali was proved by his
finding its quantity quite unaffected on his injecting
it some time after death. But this is not all,
it has also been shown that excessive cold or heat,
applied to a liver immediately after death, is also capa-
ble of checking the transformation of the amyloid. Having
killed an animal suddenly, opened its abdomen & cut off
a slice of liver which was thrown into a freezing mixture,
he found that the change of the amyloid was arrested, while
the part remaining in the body presented of course the
usual reaction in a short time. Nay further, he found
that a boiling fluid was capable of effecting the same thing,
most likely by coagulating the materials capable of acting
as ferments, but in this case the liver must be cut up
into small pieces to enable the boiling H2O to get at it at once.
Bernard had noticed also that the livers of cold blooded animals
as the frog contained sugar, or not, according to their temp=

related

at death, but his explanation of it was that it depended on an alteration in the activity of the glycogenic function, by increasing & diminishing the activity of the circulation. A similar fact too has been noticed in warm blooded animals, whose cords were cut below the origin of the phrenic nerves, that the temperature falls rapidly, & if it be kept in a cold place, that the liver immediately after death contains no sugar. That this is due to the fall in the temperature diminishing the rapidity of p. mortem changes, seems abundantly proved by the fact, that, if the heat of an animal similarly treated be kept up by warmth & artificial respiration, the liver at death will exhibit the usual reaction, unless precautions be taken to prevent the formation of sugar. All that is necessary for the change of amyloid into sugar during life is its passage into the blood, but that this process only goes on to a very small extent during life is now evident. Comparing the extent of its formation, with the large quantities of it stored up in the liver, we must see at once that the disproportion is so great as to make it pretty evident that it must serve some other purpose in the animal economy; altho' this has not yet been satisfactorily settled. A strong proof of its being capable of conversion into other articles exists in the fact Petty discovered, that the injection of a solution of $NaOCO_2$ during life into the portal vein

* Thus in a lion ½ oz in weight, considering the loss of 1½ pts Hepatine equivalent to the production of ½ sugar, (as he had previously shown) if the whole the hepatine had been converted into sugar there should have been 150 grs of it.

§ Pavy explains the conversion of the hepatine into other substances as being probably effected by a process of the nature of catalysis.

**. If a mixture of hepatine & sugar be placed in endosmotic apparatus on one side of a piece of bladder, the hepatine does not pass thro' it at all, or only in very slight degree, while the sugar diffuses itself at once.

†. Pavy indeed admits that by chemical agency there may be a slight change of sugar into lactic acid, but it is not to any appreciable extent, at least by chemical reagents.

causes an entire disappearance of the hepatine without any possibility of the whole of it having been converted into sugar, otherwise it would have been found abundantly both in the liver & blood.* So far as this point being the case, that the amount of sugar discoverable is not more than we should have expected from the $C_{12} H_{13}$ which was administered previous to the injection. The products into which the hepatine is converted have not yet been detected.§

One of the strongest objections to the generally received theory of the rapid passage of sugar into the blood, seems to me to rest on a physical fact, viz., that the amyloid, far from being an easily diffusible substance like sugar, only with difficulty passes through animal membranes.** Consider what would be the result if large quantities of sugar were being constantly formed in the hepatic cells, & passing into the blood; granting with Bary that no destruction of the sugar takes place either in the lungs or elsewhere in the body†, & with Von Becker that no higher quantity than 5 p. cent, (according to others 3 p. cent,) can exist in the blood without giving rise to glycosuria. Why the result would be that the normal quantity of sugar in the urine would be so augmented, that everyone would be diabetic even on an

animal diet, when according to the experiments of Kühne the blood of the hepatic vein contains as much as .821 p. cent of sugar & after a farinaceous diet as much as 1.128 p. cent.

It must be recollected too that the small quantities of sugar found in the right side of the heart by collection during life have not all come directly from the liver. It contains also that which has been sent thro' the body in the arteries, & returned by the veins without distinct diminution in quantity, except that small amount we now know to be drawn from the renal arteries by the kidneys.

Having now as I think dwelt sufficiently long on the proofs militating against the idea of a glycogenic function in the liver, I will pass on to consider what modifying effect on the production of sugar may arise from various physical & vital causes.

In a physiological state it seems undoubted that the circulation goes on thro' the liver in such a manner as to cause but little disturbance of, or escape of the hepatine—, a fact which would scarcely be found true if sugar, so easily diffusible, were constantly being produced in the hepatic cells. But we will find that certain circumstances are capable of effecting an alteration in this normally quiet state, &

* Another proof that the escape of amyloid is due to a physical cause in the last cases is found in the fact that if the liver be made oedematous by the injection of a quantity of H2O after death, a similar escape of amyloid is the result.

§ According to the glycogenic theory we would expect less evolved of more sugar under these circumstances, as it seems to result from the abnormal condition into which the liver is put as regards its envelope

one of these is the congestion produced in the liver by any cause either acting on the flow of blood to, or hindering the exit of the same from the liver. Under such circumstances (e.g.) as muscular exertion with obstruction to the breathing, the circulation thro' the liver becomes congested, & an escape of amyloid takes place into the blood, either by the pressure of the blood on the hepatic cells, or by the violent action of the abdominal muscles, from the obstruction of the breathing, on the organ itself. Such an escape of amyloid & consequent glycosuria, has been noticed in pertussis, pneumonia, & Coma, & is most easily explicable on the above mentioned theory, - & in a similar way we may explain the effect of section of the cervical vagi & the use of $C_2 H Cl_3$ - in both of which we find the two circumstances favourable to the escape of amyloid, - the obstruction to breathing, & the long continued, often violent muscular exertion.*

That the blood in the normal state must exert some effect in retaining the amyloid in its proper condition, was ingeniously proved by the effect of ligature of the portal vein. When this was done it was found that the sugar throughout the system generally was greatly increased - a fact which seems at least to disprove the idea of Harley that the stimulus for the production of sugar probably arises in the portal blood itself. cf. §

By far the most important modifying agent in respect to the amount of alteration in the sugar produced is certainly the nervous system. Bernard's experiments had long proved this. But instead of considering the medulla as the regulator of the production of sugar, Pavy is inclined to think that it rather supplies the force necessary to keep within very moderate bounds the chemical tendency of the amyloid to pass into sugar. In correspondence then with this theory he would explain the effects produced by Bernard's famous experiment of puncturing the medulla, as produced not by an exaltation, but by an actual loss of nervous power, with its consequence of escape of amyloid into the blood.

How is this force transmitted to the liver we ask?

After division of the vagi & cord a diabetic state does not invariably result, & if it does, is probably due to other causes than the loss of any supposed nervous influence transmitted by them. It must then descend thro' some other channel, & accordingly Pavy finds that if the whole head be cut off & artificial respiration kept up for a time, a saccharine state of the urine will result. The only other nerve channel open to it is the sympathetic, but he was rather puzzled to find that section of the cervical cord of the sympathetic had no effect. Removal of the sup. & Middle cervical ganglion however, has & also the division of the nerve filaments ascending from the sup. thoracic ganglion

* Schiff indeed seems inclined to believe that the nerve fibres
supplied by the vaso motor nerves of the abdominal organs,
he says arise in the thalami optici & cerebral peduncles
& descend thro' the medulla & down the anterior colum
of the cord emerging at the roots of the sympathetic to
supply the vessels. When the floor of the 4th ventricle
pricked there follows an enlargement of the vessels, &
escape of hepatine, but if the ant. column of the
cord be cut, the influence does not descend, & no diabet
results.

to the vertebral canal did cause Diabetes - But that this glycosuria did result solely from the stoppage of the nervous influence is not yet distinctly proved, for the injection of carbonate of soda into the circulation previous to the division of the sympathetic nerves prevents any Diabetes.*

Whichever theory may turn out to be the correct one it is evident that as yet no decided opinion can be given with regard to the real agency of the nervous system.

Before proceeding further we must give a summary of the results arrived at by Pavy -

I He has, I think, proved, that during life at least, the liver contains only a trace of sugar, but a large amount of Lepatine.

II. This Amyloid is augmented greatly by saccharo-farinaceous diet. According to the old theory then we have the anomaly of sugar into glycogen, & glycogen back to sugar again.

III No appreciable difference is discoverable in the amount of sugar in the blood in any part of the system during life.

IV. In a physiological state the least diffusible powers of Lepatine prevents its escape into the blood in any quantity. If it doth, & from various disturbing causes during life, an a conversion of amyloid into sugar takes place, & this from its diffusibility at once escapes into the blood. ——

The experiments upon which these conclusions are founded have been conducted with so scrupulous a desire of avoiding error, that they appear to me to be quite sufficient in

themselves to do away with the old theory. They have however been unprepared by Drs Harley & Sharpey, & we must accordingly briefly review their objections.

Having first satisfied themselves that sugar is to be found in the blood of dogs fed even exclusively on meat they proceeded to test the reasons for the denial of the glycogenic function. They found that the solution obtained from a slice of the liver of a dog fed 48 days on meat solely, & plunged into a freezing mixture after the animal had been killed by pithing, contained sugar, as did also the filtrate derived from a slice of the liver plunged into acidulated boiling HO. The quantity in either case was small, & great precautions were taken to get a clear filtrate in order that any, even the slightest reaction might be seen. Now Pavy himself never at any time denies that a trace of reaction may, under these circumstances, be got. In fact it is evident that the blood of the liver, - both portal & hepatic, - must contain sugar, as it does so normally even tho' the animal be fed on an azotised diet. I am not a little doubtful too as to whether the plunging of the frozen slices of liver into a boiling acidulated solution, as Harley did before testing, might not have a very opposite effect to what he imagined viz lessening the probability of finding no sugar. I am inclined to think that the action of a boiling solution on the frozen slices would be to raise the

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Dr Pavy's own experiments he had cut the slices into small bits, & rapidly mixed them about in the freezing mixture. When had frozen the pieces are removed, cut still finer, & then reduced to pulp in a mortar, & finally thrown, little at a time into the boiling liquid. Plenty of amyloid is then found but only a trace of sugar. The rabbit he found to be better than the dog for this purpose on account both of its abdominal walls & its liver being thinner. Harley employed dogs in his experiments.

temperature so gradually as really to favour, rather than otherwise, the production of sugar.* for Pavy has pointed out, how necessary it is to expose every part to the action of the boiling 110 o freezing solution at once, if we wish to prevent the formation of sugar, & this does not seem to have been sufficiently attended to by Haley.

In another experiment in which a powerful dog had been killed by section of the medulla after 72 hours starvation —; blood was collected from the —

(a) The Vena Portae —

(b) Right Side of Heart.

(c) from a portion cut off liver.

(d.) from aorta & inferior vena cava.

It is not denied that each of these bloods contained a trace of sugar, but it was said, unequivocal evidence of it was only got in that from the liver, fact which seems to me rather to confirm than oppose Pavy's observations. It is evident that the ligaturing so many arteries & veins, & the collecting of blood from the various sources mentioned, must have taken some time, & consequently any results follow from it that we would expect if Pavy's observations, as to the rapidity of change of the hepatine & the passage of sugar into the blood after death, be correct. Of the glycogenic theory on the other hand had been true, we would have expected

* The three days of starvation to which the animal was exposed before being killed could not have had much effect on the amount of glycogen, for Bernard found as much as 0·93 per cent of sugar in the liver of a dog which had been starved 4 days, & even after 12 & 15 days complete abstinence of food he has found sufficient traces of sugar in the livers of dogs.

to have found nearly as much sugar in the hepatic vein, ante & inf. vena cava as in the liver, from the fact that so long as glycogen was secreted* & being transformed into sugar according to the old theory, so long would we expect, on account of its great diffusibility to have found it in the blood of the system generally. The fact too that the blood in the right side of the heart was "doubtful" which Harley applies as a proof of the correctness of the Bernard idea, seems to me to be exactly opposed to it;— for the amyloid tho' it had time after death to become converted into sugar & pass into the blood in the liver itself, so as to be detectable in notable quantity there, could not have possibly reached the right side of the heart, especially as the portal vessels had been ligatured, & its flow thus in great measure retarded, & also on account of most of it having escaped into the abdomen when the first slice of liver was cut off. These experiments then, the only ones I know of as yet having been published to disprove the correctness of Pavy's experiments, do not confute them, & think, in the smallest degree, in turn add support to the original glycogenic theory ———

But while his observations have been attacked, they have on the other hand also been confirmed by Mr. McDonnell §, but he seems to think that the

final destination of the amyloid is very different from what Parry imagines. He points out strongly the fact proved by Lehmann that the fibrine & albumen of the portal blood seem to be used up in some way by the liver, & seems to believe that coincidently with this process of desintegration, a form of reconstruction is continually going on in the liver, & that the N. of the desintegrated compounds, - (the amount in the bile not being worth taking into account,) may be united to the non azotized hepatine, which instead of normally escaping as sugar, enters into the hepatic blood as a nitrogeneous constituent of its protoplasm, partly he thinks as a substance resembling globuline in some respects, in others, albuminose.

If we examine the tissues of the foetus after the 4th or 5th months, or the placenta of many animals, as long before shown by Bernard, we will find them regularly loaded with a substance closely resembling the amyloid of the liver. That this substance in the foetal tissues is gradually converted into the highly nitrogenous principles of muscle, there can be little doubt. Mr. W. Bunell is therefore of opinion that the liver may be quite able to do for the adult, what the tissues in general do for the foetus, & unite the N. derived from the desintegrated fibrine, - seeing that it cannot altogether escape [illegible] with the

bile, — with the hepatine. To support this theory he attempts to show that in proportion to the amount of fibrine which disappears, the quantity of N. in the bile is very small indeed; but that the colorless corpuscles of the blood in its passage thro' the liver become greatly augmented, & at the same time it seems to contain a new azotized compound resembling somewhat casein. During active digestion at least the hepatic blood contains a much larger quantity of this than arterial, & the latter in its turn more than the portal. Along with this we find a great increase in the colorless corpuscles, a fact long known to physiologists. So great is this increase that the formation, or reconstruction of colorless corpuscles has been considered by some as one of the most important functions of the liver. Altho' it is but thereby that the idea of the liver being a blood forming organ is not a new one, yet it still seems to me a very doubtful hypothesis that a substance, in all respects resembling pleuch, should take to itself, within the liver, N derived from the metamorphosis of albuminous compounds, & become there converted either into a material resembling a colorless blood cell, or even casein. When the much closer relations between hepatine & fat, & the fact of the

formation of the latter being so much increased by the ingestion of large quantities of starch & sugar, the ultimate destination of the latter will, I think, more likely be found to have some connection with the production of fat. The rapid emaciation & loss of fat in Diabetic patients, in whom the starch & sugar either are not converted into amyloid, or in whom the amyloid passes out of the system as a useless material after its conversion into sugar, seems to me to bear strongly on the point in question, — but the subject is one, the unravelling of which will require the skill & ingenuity of the ablest physiologists.

Having thus reviewed the present state of our knowledge of the so called glycogenic function I pass on to a short sketch of the pathology of a disease, which ought not only to be interesting to us on account of its frequency, & so often disastrous results, but also on account of its connection with those very physiological subjects we have been engaged in reviewing. —— ——

Diabetes, —— the name first given by Aretaeus to indicate that class of diseases in which there was an excessive excretion of urine, must necessarily have included many besides the one with which we have at present to do. On fast without interrup

* About 1844 Mialhe offered what then appeared to be a rather ingenious chemical explanation of the cause of the disease in question. It had long been known that sugar is destroyed in the presence of an alkali. Consequently, he thought, if the sugar introduced into the circulation does not find the alkalinity suitable for its destruction, it will accumulate there, & be excreted in the urine. Hence the proper treatment according to this theory would be the administration of alkalies.

into a history of this disease we may simply state that it was not till 1672 that sugar was discovered in the urine by our countryman Dr. Willis, & more than a century & a half elapsed before this was known to be identical with grape sugar. Towards the close of the 18th century Rollo — in accordance with the physiological notions of his time, which attributed to the gastric juice the power of changing according to the nature of the food it had to digest — being athelin with an animal, acid with a vegetable diet, — ascribed diabetes to an alteration in the digestive processes, due to the pretended power he imagined the gastric juice had acquired of changing vegetable aliment into sugar, & hence arose the plan of treatment which has come down to us under his name.* Such a view of course was founded on very erroneous physiological ideas, but the true causes of it are still very obscure.

Let me here observe that one important point in reference to this disease has not yet been so strongly pointed out as it ought to have been, viz, that glycosuria, like albuminuria, is merely a symptom consisting in an increase of the normal constituents of the urine to such an extent, as, if persistent, to give rise to very formidable, & ultimately, usually fatal results —

* A similar appearance has been noticed in persons who have died of other complaints accompanied by an increased flow of urine, & also if, from any cause, the action of the kidneys has been prevented during its work. Bernard has also noticed inflammation & the formation of little abscesses in the Kidneys of a rabbit, into whose veins sugar had been injected.

§ Q am inclined to think that the state of the liver will depend upon whether the patient dies suddenly or by a slow & gradually declining, for while the liver in the first case has been found very large, engorged with blood & charged with sugar, if the suffering slow & gradually with the patient, no hypertrophy or sugar will be found.

Are there any really satisfactory appearances found in the bodies of patients who have died of this disease? —
Observers have almost invariably mentioned the hypertrophied & vascular appearance of the Kidneys, — a circumstance amply in accordance with the increased work they have to perform & nothing more.* Others have occasionally noticed a thickened & vascular state of the Stomach, — which we cannot wonder at considering that it is usually called on by such patients to do double work. It has indeed been asserted by Wilks that the liver is more homogeneous & firmer than usual, as also darker in color, but Griesinger on the contrary maintains that that organ is in no way altered, & that he has not been able to detect any microscopic changes in it.§
I think then it must be evident that we cannot ascribe the disease to any organic structural alteration of the liver substance, & that it ought to be ascribed to some alteration in its functional activity as indeed Bernard's idea. He imagined that there was an exaggeration of the functional activity of the liver leading to a production of sugar in excess of its power of destruction, & that this exaggeration of sugar formation may be due either to an increase in volume of the organ itself, or perhaps to an increase in the quantity of sugar contained in its tissue.

* This view is supported by the fact that the glycosuria ceases altogether sometimes almost as soon as the diet is made exclusively animal.

The cause to be adduced might be either in the liver itself, or external to that organ, as e.g. in the nervous system. Of the glycogenic theory then to be incorrect as being founded on a P. mortem condition of the liver, his explanations fall to the ground. Another idea was that the production of sugar in the liver might indeed remain the same, but that there was some impediment offered to its normal destruction, but as this destruction is nowhere known to take place, this theory falls to the ground also.

Let us see therefore what explanation of the phenomena of this disease may be offered in accordance with the theory of the formation of amyloid substance in the liver, & the views of Pavy. If the liver from any reason was incapable of acting upon & assimilating the sugar derived from the saccharo farinaceous articles of our food, it must necessarily pass thro' the system as a useless, & undoubtedly in these large quantities, as a pernicious ingredient of the blood, to be excreted by the kidneys, & produce glycosuria.* What the assimilating power of the liver even in a healthy state is not unlimited, we know well from the simple fact, that excess in diet, such as eating too large a quantity of asparagus, (Harley) or beans, or in fact of any saccharo farinaceous articles may cause an increase of sugar to such an

* It sometimes happens that in this second class there may be deception on the part of the patient, from his concealing the fact of his taking some saccharine or farinaceous article. It used to be thought that more urine was passed than could be accounted for by the fluids they took, but Dr. Basham found that when the patients were separated, strictly watched, & as much 40 grains as they chose to drink, no more urine was passed than could be thus accounted for.

§ The smallest quantity of sugar sometimes seems to act in Diabetics, producing an increased excretion of amyloid, as Prout noticed.

extent as to give rise to a temporary Diabetes. In some cases it is evident that no more sugar escapes by the kidneys than may be accounted for as taken in the food, but there is a second class in whom this want of assimilative power for sugar is combined with something more, for in this urine we can find more sugar than is actually taken in the food;* & in a third class of cases again it appears that the saccharine element may be taken up to a certain extent, although that certainly a small one, without producing glycosuria.§

It is evident however that this defect in the assimilative power will not explain all cases, for we often find that the sugar continues to be passed in some amount even when all saccharo farinaceous articles are strictly excluded. The amyloid itself it is true may be formed from albuminous substances, but we have scarcely any evidence that albuminous matter may be decomposed into glycose & urea, as the Bro. Dr. Haughton maintains, in the blood. In such a case we may believe that the amyloid passes into sugar from some perverted action of the function of the liver. Experiments indeed have shown that such a congestion of the liver as may be caused by imperfect respiration, or obstruction to the flow of blood from the liver, may cause an increased escape of amyloid into the blood, & that many diseases causing embarrassment to the breathing

† Phlebitis according to most. According to Parry & Wilks
however it is a chronic inflammation leading to the
formation of cavities. Probably both occur.

§ Out of 4 Diabetic patients I have examined, this
was the only case assignable in two.

+ obstruction to the circulation acts in a similar manner. But altho' in the last stages of Diabetes there may be a diseased state of the lungs, this is not generally the case at first. I am disposed to believe that this diseased state * is a consequence of the Diabetes, resulting from an altered state of the blood, deeply affecting the processes of nutrition. It is in this way that I think we may at least in part satisfactorily account for the rapid progressive emaciation + loss of flesh + strength in such patients, even tho' indulging in large quantities of animal food.—

But the real causes giving rise to this disease still remain without a clue to their solution, for altho' we have imagined it to be traceable to cold in many instances § we are still in ignorence as to how this acts. It has been said to be an hereditary disease, + this seems in some cases to be true, + again Dr. Prout has noticed it in gouty + dyspeptic people. A temporary Diabetes has been produced mechanically, in at least one case we know of, in which the kick of a horse on the right hypochondrium gave rise to it. In this case it might be due to rupture of the liver cells + escape of amylaid into the blood. It is undoubtedly often dependent on cerebro spinal lesion, + in illustration of this we may give the following cases.

(a). A little girl was brought into one of the London Hospitals with fracture of the base of the skull. She died [illegible]

Yours

* Another idea was that it might be ascribed to a pressure
any influence on the circulation thro' the liver, and
which, the obstruction to breathing such an injury
produces, might cause.

hours afterwards, & on examination, the urine in the bladder was found porcelaine. There was an effusion into the floor of the 4th ventricle in this case, to which I am inclined to attribute it.* One another case that of a medical gentleman who had an attack of apoplexy followed by hemiplegia of left side, Diabetes showed itself in 3 weeks. So frequently indeed is it connected with cerebral lesion that Dr Marshal endeavours to show, that such lesions are frequently the consequences, & not the the causes of Diabetes, thinking it quite possible that xx the disease might give rise to hemi- or paraplegia just as it does to cataract. One the case of a female who had been Diabetic for 7 years, & who suddenly perished of a cerebral attack, I found a superficial ulceration between the back part of the left optic thalamus & the corpora quadrigemina, which I was inclined to ascribe to the Diabetes. I think however that this idea is by no means supported by the actual facts & cases brought forward, & the coincidence, in such a long standing Diabetes, might be only a coincidence.—

But there are sufficiencies that the presence of sugar in the blood causes considerable alteration in the nutritive processes. It is a well known physiological fact that the natural relationship between

the blood & the tissues is one of the great aids in maintaining the circulation. The presence of a large quantity of sugar in the blood probably modifies this relationship in no small degree, & may render the blood unfit for the healthy discharge of its functions, & thus cause many of those structural & functional disorders so common among Diabetics. Thus it is that we may account for those cavities, formed by the breaking up of lung tissue, so common in the latter stages of Diabetes, & also for the production of cataract in many patients affected with this disorder - Direct experiments indeed seem to prove that the latter is very intimately connected with the presence of sugar in the blood. Dr Mitchell observed that the injection of sugar under the skin of a dog caused a variety of cataract due to an alteration of the form & relative position of the fibres of the lens. Dr Richardson from his experiments, seems to maintain that the cataractous state is produced by endosmosis, & that if the lenses were removed when quite opaque sugar could be found in them; but if this were the case the cataract would not be so strictly confined to the back of the lens, & according to Recaché no sugar is to be found in the lenses in such cases, nor could he produce cataract by injecting sugar into the aqueous chamber. It is therefore more probably to be ascribed to a mal-

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To a similar circumstance we ascribe the increasing phag-
enges, dry & cracked skin & gangrene which sometimes
occurs.

nutrition,* to the more general & extended effects of which death may often be ascribed.

No doubt there may be more to account for the rapid emaciation & debility produced, than the mere loss of a valuable ingredient of the food & the presence of sugar in the blood, but as yet we can scarcely explain why one patient should get so much worse than another, even tho' not allowing so much sugar to escape by the urine. Indeed tho' it is evident that we are not yet able to fathom the true causes of this disorder, it should be our utmost effort to gain a correct knowledge of the physiology of the subject, remembering that without such knowledge we will strive in vain to elucidate its true pathology. It is only when these 2 cognate sciences go hand in hand, that we can hope to make progress, or see the day when the pathology of such a disease as Diabetes will be clear to us -

When, but not till then, can we expect to see the treatment at present directed to the alleviation of symptoms, become really efficacious in relieving, & even in restoring to health, those of our fellow creatures who suffer under this painful malady.

Lauchlan Bitten.