On some points connected wit the pathology and treatment of diabetes / by A.E. Wright.

GROCERS' RESEARCH SCHOLARSHIP LECTURES.

ON

Some Points connected with the Pathology and Treatment of Diabetes.

Delivered in the Theatre of the London University.

By A. E. WRIGHT,
B.A. Trin. Coll., Camb.; M.D. Univ. of Dublin,
Late Grocers' Research Scholar.

London:
JOHN BALE & SONS,
87-89, GREAT TITCHFIELD STREET, OXFORD STREET, W.
—
1891.

GROCERS' RESEARCH SCHOLARSHIP LECTURES.

ON

Some Points connected with the Pathology and Treatment of Diabetes.

Delivered in the Theatre of the London University.

By A. E. WRIGHT,
B.A. Trin. Coll., Camb.; M.D. Univ. of Dublin,
Late Grocers' Research Scholar.

London:
JOHN BALE & SONS,
87-89, GREAT TITCHFIELD STREET, OXFORD STREET, W.
—
1891.

Grocers' Research Scholarship Lectures.

ON

Some Points connected with the Pathology and Treatment of Diabetes.

Delivered in the Theatre of the London University.

By A. E. WRIGHT, B.A. Trin. Coll., Camb.,
M.D. Univ. of Dubl.
Late Grocers' Research Scholar.

Examination of the Question as to whether all Sugars are the same in their Effect on the diabetic Organism.—Resultant Classification of the Sugars into (a) *Innocuous,* (b) *Hurtful, and* (c) *Mixed.—Examination of the Conditions under which the Hurtful Sugars are Assimilated.—"Assimilation Quantum" and "Assimilation Ratio."—Conditions pointing to Admissibility of Allowing some Carbohydrate.—Proposals for giving Maximum of Carbohydrate consistently with Minimum of Sugar Excretion.—Sugarless Milk for Diabetics.—Method of Preparation.—Exhibition of Alkalies in Diabetes.—Indications for in Certain Cases.—Phloridzin Diabetes: resemblances to Human Diabetes.—Proof that the Sugar is Derived from Proteid of Body. Wooldridge's Coagulation Method, bearing upon Study of Conditions of Venosity of Portal Blood in Diabetes.*

[After some introductory remarks, in which he referred to the complexity of some of the questions which might be raised, the lecturer first turned his attention to a simpler problem, and continued as follows:—]

The accompanying table contains a clinical classification of the most important sugars. We have to set ourselves to inquire whether that classification is of any importance to us as pathologists and physicians. We shall begin by taking first dextrose and levulose. These two sugars—dextrose and levulose—are the two halves into which ordinary cane-sugar splits up. These halves are indistinguishable from each other by our ordinary senses, and by our ordinary sugar tests. The polarimeter, however, shows them to be different, the dextrose half turning the plane of polarised light to the right, and the levulose half to the left. Now, the man to whom the honour belongs of having asked and answered, not only this particular question, but more of such questions in regard to diabetes, than any other man, is Professor Külz, of Marburg, under whom I had the privilege of studying for some time.

CARBOHYDRATES.

I. *Monosaccharids* ($C_6H_{12}O_6$):
1. Dextrose (*a*).
2. Levulose (*b*).
3. Galactose (*c*).

II. *Disaccharids* ($C_{12}H_{22}O_{11}$):
4. Milk sugar (*c a*) { dextrose (*a*) / galactose (*c*)
5. Cane sugar (*b a*) { dextrose (*a*) / levulose (*b*) } invert sugar.
6. Maltose (*a*) { dextrose (*a*) / dextrose (*a*)

III. *Polysaccharids* ($C_6H_{12}O_6$) n ± m (H^2O):
7. Dextrose group (*a*): starches (*a*): dextrins (*a*).[1]
8. Levulose group (*b*): inulin (*b*): levulin (*b*).

(*a*) Unassimilable hurtful sugars. (*b*) Assimilable innocuous sugars. (*c*) Insufficiently studied sugars.

With respect to this particular question, Professor Külz succeeded in establishing that levulose does differ from dextrose in its effect upon the diabetic organism. Levulose is assimilated by the diabetic patient, whereas his organism has, at any rate partly, and sometimes perhaps entirely, lost the power of assimilating dextrose. The chemistry of the sugars has thus become of extreme importance to the physician. The effect of a complex carbohydrate upon the system is the sum of the effects of the factors of that carbo-

[1] Placed in this category on chemical reasons alone, as there are no clinical experiments with it yet forthcoming.

hydrate when reduced to terms of monosaccharids. Thus cane sugar can be split up into equal quantities of dextrose and levulose. Maltose, on the other hand, splits up into two molecules of dextrose. The third disaccharid, milk sugar, breaks up into equal weights of dextrose and galactose.

The third great group of the carbohydrates, the polysaccharids, falls naturally into two great subdivisions, one which includes glycogen and the starches, and the dextrins, which are the intermediate products obtained in the course of the dissociation of starch into simple sugars. All the members of this division yield only dextrose as their ultimate resolution product; they contain no levulose at all. Over against these we may set the group of polysaccharids which yield only levulose when they are broken down into simple sugars. The principal representative of this class is inulin. Levulin may also be classed under this group.

We find that there is at present among clinicians a universal consensus of opinion that the carbohydrates in the food of the diabetic patient must be restricted in order to avoid poisoning the system by the presence of large quantities of unassimilated sugar. Further, we find (and this is but the natural outcome of the good results obtained by restriction) that some clinicians have insisted that carbohydrate food should be absolutely prohibited to the diabetic in all cases where it should prove at all practicable to carry this out. What has resulted from such absolute restriction has, however, not always been unmixed good. It has been shown that although the sugar is thus reduced to a minimum, other morbid products, such as acetone and oxybutyric acid, appear or increase in quantity in the urine. It follows, therefore, that total abstention from carbohydrate food is not always a counsel of perfection for the diabetic patient.

If I might venture to express an opinion on so intricate a subject it would be that the ideal diet would be a diet of proteids and fats, to which the innocuous lævo-rotatory carbohydrates had been added in such quantities as were available, or in default of these the "assimilable quantum" of dextro-rotatory carbohydrates, at least whenever the bad results of a proteid diet were manifesting themselves.

I may, perhaps, remark in passing that the importance of the fats in the diabetic dietary does not seem to have been emphasised sufficiently in this country.

It will follow from what has been said about the sugars

that we may divide them clinically into three classes: (1) the innocuous sugars; (2) the hurtful or relatively unassimilable sugars; (3) the mixed sugars. Such sugars as galactose, which have as yet been insufficiently studied from a clinical standpoint, must at present be referred to a kind of indeterminate limbo.

Of the entirely assimilable class of sugars we have only two: levulose, which, as far as is at present known, does not occur by itself in Nature, and which we may, therefore, dismiss from our consideration; and inulin. Inulin is a homologue of starch, with the important difference that, instead of yielding dextro-rotatory simple sugars, as starch does, it yields only lævo-rotatory simple sugars. It occurs abundantly in dahlia tubers, in dandelion, chicory, and other roots, and, as Külz pointed out years ago, it can be baked into a good bread. Against it there is chiefly its price, some 15s. per pound; but, as Külz again suggested, there is no reason why it should not be produced at a comparatively moderate price. When the fact becomes widely known that there would be a large demand for it if it were cheaper, the first step will have been taken towards its being produced for the market. At present, I am sorry to say, an innocuous—that is, entirely assimilable—sugar for dietetic purposes remains as yet an unrealised desideratum.[2]

Not being able, therefore, to give the best thing in the way of carbohydrates to our patients, we have in certain cases to inquire what is the next to best. This I spoke of above as the "assimilable quantum" of dextro-rotatory carbohydrate. If we are dealing with a diabetic who is excreting no sugar on a diet from which all carbohydrates have been excluded, we might find his urine to be still quite free from sugar after we had allowed him, in addition to his previous diet, 25 grammes of dextrose, or its equivalent in whatever carbohydrate he might prefer. In such a case, 25 grammes would be within the patient's assimilation quantum, which might turn out to be, say 30 or 40 grammes. In a case like this, if the morbid products

---

[2] We may, however, possibly have an approach to such a food stuff in the Jerusalem artichoke, the carbohydrates of which, according to Tollens, are levulin and inulin during the spring and summer, while dextro-rotatory carbohydrates make their appearance, in the tubers only, in the autumn.

referable to proteid metabolism were at all inclined to dominate the situation, I would urge that the patient should be allowed, as a substitute for some part of his proteid food, a certain amount of carbohydrate, provided that the quantity allowed was well within the patient's assimilation quantum. This limitation is to be observed where at all practicable, because when the patient is allowed carbohydrate to an amount at all approaching his assimilation quantum, it is found that that assimilation quantum has a tendency to diminish.

I have hitherto used the term "assimilation quantum" as if every diabetic had an appreciable quantity of dextrose he could assimilate without secreting sugar. This obviously cannot be the case in the severe form of diabetes, in which the patient continues to excrete sugar even although he may be taking none. But, on the other hand, there is reason to believe that no diabetic patient, even of the severe form, excretes all the sugar he takes in in his food. He is, in fact, almost exactly in the same position with regard to sugar excretion that the diabetic of the lighter form is when he has been given sugar in excess of his assimilation quantum. Let us suppose, to take the facts of an actual case, that we had given a diabetic patient, whose assimilation quantum we had found to lie somewhere above 25 grammes of dextrose, 50 grammes of that sugar, and then found his urine to contain 6 grammes of sugar. If we now proceeded to give him 100 grammes, his dextrose excretion would not be increased by another 50 grammes, but only by another 3 grammes. It would amount to only 9 grammes in all. Evidently therefore when we have overstepped the limits of the assimilation quantum, we have to deal with a ratio between assimilation and excretion. We may call this ratio the assimilation ratio, and we have to deal with an assimilation ratio both in the case of the slight form of diabetes, where sugar in excess of the assimilation powers is taken in in the food, and also in case of the severe form of diabetes, where the urine is never free from sugar even in the strictest diet. In the patient referred to above the assimilation ratio for 50 grammes may be represented by $\frac{44}{50}$, and for 100 grammes as $\frac{91}{100}$. The ratios in this particular case are, as will be seen, very favourable ones.

With reference now to the question of giving carbohydrates in the severe form of diabetes, I think something

may be ventured in that direction as long as the assimilation ratio is moderately high, and as long as what I have called the morbid products of proteid metabolism are urgently requiring attention.

I would desire, however, not to be misunderstood on this point. It is only when there is urgency of this kind that an increase of sugar in the urine should be permitted. In other cases it is only a weak pity that would allow a diabetic unnecessary carbohydrate.

We have no knowledge of what I have from the clinical standpoint called a mixed sugar in the chemical class of the non-crystallisable polysaccharids. They either fall entirely within the class of assimilable or of hurtful sugars. When, however, we come to the group of the disaccharids we meet with two examples of mixed sugars, cane sugar and milk sugar. The third of our disaccharids, maltose, of course falls entirely into the class of the hurtful sugars. Cane sugar, on the other hand, is composed of an innocuous and a hurtful sugar. From this chemical constitution, therefore, an important practical point results, namely, that two parts by weight of cane or invert sugar contain less unassimilable sugar than one part by weight of starch. This means that we may allow fruit in diabetes a great deal more readily than we may allow bread, and it shows that in the selection of vegetables for the diabetic patient we should choose such as contain as much of their carbohydrates as possible in the form of cane sugar. With regard specially to such fruits as grapes, the sugar of which is almost entirely invert sugar, it is wonderful how little harm results to diabetic patients from eating great quantities of them.

Milk sugar consists of equal parts by weight of dextrose and galactose. If galactose is an assimilable sugar, a point which has not yet been certainly made out, milk sugar would also fall into the category of the mixed sugars. There are considerable difficulties in the way of ascertaining whether galactose is assimilated or not. To begin with: there is the difficulty of getting it pure in large quantities; and then more especially there is the difficulty of ascertaining how much of it is actually absorbed as such, seeing that it breaks down very readily into lactic acid. This source of error, which affects the determination of sugar assimilation in the case of every one of the carbohydrates, makes itself particularly felt in the case

of galactose and of milk sugar. Hence the results that Külz has obtained in his study of milk sugar vary extraordinarily. Sometimes milk sugar appeared to produce very little sugar in the urine, sometimes it produced a great deal.

It is therefore plain that the question about the assimilability of galactose cannot be settled without a large number of observations. In dogs, according to Hoffmeister's observations, milk sugar appears to be the least assimilable of all sugars. The general result of the observations made in man in this: the addition of milk sugar to a diabetic diet in almost all cases seriously increases the amount of sugar in the urine. This is obviously what its chemical constitution would lead us to expect, seeing that it contains 50 per cent. of dextrose. Whether it is more or less assimilable than cane sugar must remain for the future to determine.

When we come to the practical clinical side of the matter, we find that milk, because of the 4 per cent. of milk sugar it contains, has been steadily forbidden to the diabetic by the great majority of clinicians. The treatment of diabetes by skim milk, which is proposed by Dr. H. B. Donkin, need, perhaps, not be discussed here. It has no doubt a good deal to recommend it in the fact that the proportion of fat to proteid in a milk diet, even in skim milk diet, is larger than it would be in almost any other diet, and this is an undoubted advantage. The weak point, however, of the diet is the fact that the carbohydrate of milk is milk sugar, which is not a desirable element in diabetic diet.

When we come to consider, however, the very severe restrictions that have to be imposed on the diabetic in the matter of diet, we cannot help feeling some amount of regret in having to proscribe the valuable proteid and fat of milk because of the presence of the milk sugar. By putting together a few facts that have been long known about milk, I have been able to arrive at a solution of the problem. Instead of getting rid of the sugar from the proteid and fat of the milk, which I failed in doing, it was evidently possible to perform the reverse process, and to separate the proteid and fat of the milk from the sugar; in a word, to precipitate the casein and fat of the milk, to filter them off, allowing all the sugar to run away from them, and then to redissolve the washed precipitate in a

solution of the normal salts of milk, to which a little alkali had been added. The process is a very simple one. Take a quantity of milk, dilute it with three or four volumes of water, to which 1 to 2[3] parts per 1,000 of acetic acid have been added. This produces a precipitation of all the casein and fat of the milk. The precipitate is allowed to settle for a few minutes, and then strained through a piece of calico. The precipitate is then washed, and redissolved in a 1 per cent. solution of the following mixture[4] of salts :—

Sodium chloride ...	11.5 parts.	Magnesium citrate ...	4.4 parts.
Potassium chloride ...	9.9 ,,	Dicalcium phosphate ...	8.0 ,,
Monopotassium phosphate	13.8 ,,	Tricalcium phosphate ...	9.6 ,,
Dipotassium phosphate	10.0 ,,	Calcium citrate... ...	25.5 ,,
Citrate of potassium ...	5.9 ,,	Calcium oxide	5.5 ,,
Dimagnesium phosphate	4.0 ,,	Sodium carbonate ...	40.0 ,,

A trace of saccharin may be used to sweeten the milk, and the salt solution is best used at about blood temperature, and the casein and fat precipitate is to be mixed up with it, as in making cocoa, to the desired thickness. We obtain by this easy method a very fairly palatable and entirely sugarless milk. The precipitated casein and fat can also be dried without undergoing alteration, and then used for the preparation of the milk.

The indications in the occurrence of which it may be desirable to allow sugar in diabetes are the appearance in large quantities in the milk of the morbid products of proteid metabolism. Among such products are acetone, acet-acetic acid, and oxybutyric acid. With regard to the conditions of excretion of each one of these bodies, a certain number of facts have been collected—facts that raise a very strong presumption that these bodies have their source in the proteid metabolism of the body. I was anxious in the case of acetone, which is, perhaps, the only one of these bodies which can as yet be accurately quantitatively estimated, to convert the presumption of origin into more of a certainty, and so I undertook while in Australia a series of estimations of the daily excretion of nitrogen, acetone, and sugar in a diabetic case which I had

---

[3] ℥jss to ℥iij of acid. acet. fort. of the *B. P.* to Oj of water.

[4] This mixture of salts, which is based upon Söldner's analyses, is, no doubt, not the best that could be obtained, but it will do tolerably well. Some amount of insoluble salts sinks to the bottom of the vessel. The salt solution may simply be poured off from this.

under my care. It was found that the acetone does not vary either directly with, or inversely as, the sugar excretion. I think also that the results afford good grounds for believing that it varies directly with the nitrogen excretion.

Excretion of Acetone, Sugar, and Nitrogen in Urine of Mrs. S.

Date.	Quantity of Urine in 24 hours.	Acetone in 24 hours.	Nitrogen in 24 hours.	Sugar in 24 hours.	NH_3
	cc.	grs.	grs.	grs.	grs.
Aug. 31st	1,134	1.08	16.8	10.2	1.29
Sept. 1st	1,701	1.35	24.2	10.2	1.3
,, 2nd	2,268	1.37	23.4	4.5	
,, 3rd	1,701	.89	22.8	10.2	
,, 4th	1,417	.79	15.8	21.3	
,, 5th	1,701	1.05		1.75	1.73
,, 6th	1,701	1.51	17.85	15.3	
,, 7th	1,701	1.81	18.36	8.5	
,, 8th	2,268	1.94	18.73	trace	
,, 9th	1,934	1.79	15.00	4.5	
,, 28th	1,701	1.34	17.13	22.1	
,, 29th	1,701	1.49	19.50	20.4	
,, 30th	2,268	1.73	19.68	22.68	
Oct. 1st	1,134	.75	14.44	15.87	
,, 2nd	1,701	1.12	15.70	23.8	
,, 3rd	1,701	1.11		17.0	1.08
,, 4th	1,701	1.14	13.8	17.0	1.01
,, 5th	1,134	.97	12.9	11.34	
,, 11th	1,134	2.08	20.16	13.6	
,, 12th	1,701	1.30	19.08	8.5	
,, 13th	1,701		24.48	11.9	
,, 14th	1,134	1.19	21.05	13.6	
,, 15th	1,417	1.18	17.46	12.75	
,, 16th	1,134	1.32	19.45	3.4	
,, 17th	1,417	.54	17.00	7.08	

The nitrogen was estimated by Kjeldahl's method. The acetone was weighed as iodoform after having been dried to a constant weight over sulphuric acid. The sugar was estimated polarimetrically by one of Schmidt and Hänsch's polarimeters. The whole day's portion of urine was collected, filled up to an even number of pints and half pints, and a sample of two pints sent daily for analysis.

We may, therefore, take the acetone excretion as an indication, though it may not be a perfectly accurate measure of the irregular proteid metabolism, which we have good grounds for bringing into connection with diabetic coma. When, therefore, the acetone and the oxybutyric acid increase in quantity in the urine, it is high time to do something to restrain it by introducing an alteration in the diet. I have not yet sufficient observations to be able to state whether an increase of fat in the diet has a salutary influence in such cases. I have an impression, however, from the cases that I have watched, that it has such an

influence, and I hope soon to be in a position to make a positive statement on the point. In the meantime I think we are at least bound to decrease the amount of nitrogenous food in such a case, and having decreased it, we are equally constrained to find a substitute. We can find such a substitute only in increasing the amount of carbohydrates, unless we find it possible still further to increase the fat in the diet.

I cannot now go into the question of the increase of the assimilation quantum and of the assimilation ratio of carbohydrates that is brought about by muscular exercise, or into the effect of opium upon it.

The idea that the administration of alkalies in diabetes is a good routine practice is undoubtedly incorrect. In point of fact, it generally disappoints. I happen, however, to have had the care of a case where treatment with alkalies was very successful, and which appears to me interesting as showing the indications for such a treatment. The patient, who had been rapidly emaciating, was treated only by a certain restriction of diet and by the administration of alkalies, with the result that her body weight rose from 8 st. 7 lbs. to 9 st. 1 lb. in the course of the next seven weeks.

When the patient came under my charge, I proceeded as usual to estimate the amount of preformed ammonia in the urine. The urine was only slightly acid to litmus paper. That in itself was, of course, no sort of an index to its real acidity, the real acidity of the urine being the sum of this which I may call the "visible acidity"—that is, the acidity directly determinable by an indicator like litmus—together with "the latent acidity." The latent acidity is the surplus of acid over fixed bases in the urine—less, of course, that minute fraction which is immediately recognisable as the visible acidity. The surplus of acid over the amount of the fixed bases that the organism can spare for neutralisation purposes is, as the beautiful investigations of Hallervorden have shown, always neutralised in the human or carnivorous organism by ammonia before it is excreted. Thus, the amount of preformed ammonia comes to be the index of the latent acidity of the urine.

The preformed ammonia in this patient's urine in the twenty-four hours was more than six times as great as the normal average daily quantity, which ranges somewhere about 0.75 gramme. I subjoin the daily estimations of ammonia and sugar :—

	Urine 24 hours.	React.	NH_3.	Sugar.	Treatment.
1890.	cc.		grs.	grs.	
Aug. 6th	2,835	acid.	4.58	22.68	Restriction of carbohydrates in food from Aug. 7th, 1.6 gramme of citrate of potash t.i.d.
,, 7th	3,414	,,	4.64	6.8	
,, 8th	3,414	,,	3.63	13.6	
,, 9th	2,835	,,	2.76	11.3	
,, 10th	2,268	,,	3.08	0.0	
,, 11th	2,268	,,	3.08	0.0	
,, 12th	2,268	,,	2.79	trace	
,, 13th	2,268	,,	2.4	,,	
,, 14th	2,268	,,	2.12	,,	
,, 15th	2,835	,,		,,	
,, 16th	2,268	,,	1.93	2.25	
,, 17th	2,268*	,,	2.22	4.5	Same dieting, 3 grammes of citrate of potash t.i.d. from Aug. 17th, 1890.
,, 18th	1,701†	,,	1.59	17.0	
,, 19th	1,701	,,	.97	29.75	
,, 20th	2,268	alkaline.		22.68	

* For 25 hours. † For 23 hours.

The sugar and ammonia are tabulated as grammes excreted per 24 hours. The urine was filled up daily to a fixed number of pints or half-pints, and the estimations made in a sample of the whole quantity passed in the 24 hours. This is the same case as that in which the estimations of acetone reported above were made.

Recent researches on diabetes show that it requires some patient chemical study of a case to be able to treat it to best advantage.

The discovery of the phenomena of phloridzin, or, more correctly speaking, of phloretin diabetes, is due to Professor von Mering, of Strassburg. He was, I believe, investigating the effects of certain glucosides on the storage of glycogen in the liver, when, in the course of his experiments with the glucoside phloridzin, which is obtained from the bark of many of our common fruit trees, he came upon the remarkable fact that the phloridzin had made his animals glycosuric. The glycosuria is not due to a mere splitting off of the sugar contained in the phloridzin, because it can be obtained equally well when phloretin (that is, the residue of the phloridzin after the sugar has been split off) is administered. The glycosuria from phloridzin can be produced in dogs and cats and rabbits, and also in man.[5] With phloretin the diabetes occurs in dogs and cats, but I have failed

[5] In connection with this last fact, it is interesting to note that in some of our popular handbooks of materia medica phloridzin is described as "a good bitter aromatic tonic," and is directed to be prescribed in doses of from 5 to 15 grains. With this last dose, twice daily, von Mering obtained as much as 6 lbs. of sugar in the course of a month from "a patient."

to produce it in rabbits. In regard to the quantity of sugar excreted, I have obtained as much as 42 grammes (that is, more than one ounce and a third) in a dog's urine for a single day. The animals get apparently perfectly well when the administration of the drug comes to an end, and even while the sugar excretion is taking place the animals cannot be distinguished from normal ones.

Very interesting are the close resemblances between phloretin diabetes and human diabetes ; for instance, the increase of the sugar excretion in the diabetic patient of the severe form when he is given more proteid food is exactly paralleled by what occurs in phloretin diabetes. In one experiment on a cat the sugar excretion was with the same dose of phloridzin, when no food was given, 2.2 grs. per kilo. ; when proteid food was given, 6.34 grs. per kilo.

Above all interesting is the occurrence of phloretin diabetes when the drug has been administered after prolonged periods of inanition. The details of the researches I have made upon this subject under Professor Külz's guidance are, I hope, to be published by him very soon. They show, I think, beyond the possibility of a doubt that the sugar in the urine cannot be entirely derived from the glycogen that has been stored up in the body, and they therefore give countenance to von Mering's view that the sugar is derived from the body proteid.

Von Mering originally asserted that an animal becomes glycogen-free after only five days' inanition combined with phloridzin diabetes. He has in a later paper modified the statement, and added one or two additional days to his original five. Von Mering's statement that the animal becomes glycogen-free is not correct. Prolonged and repeated phloridzin diabetes combined with absolute inanition does not necessarily cause an animal to become glycogen-free ; on the contrary, there is sometimes under such circumstances still a large quantity of glycogen in the body. Nevertheless, von Mering is probably right in the main in deriving the sugar in such cases of phloridzin diabetes from the body proteids, even although the particular proof he adduces can easily be invalidated. The proteid derivation of the sugar may be safely assumed from such considerations as the following : Given an animal after prolonged inanition, and given the quantity of sugar excreted in the urine during the phloretin diabetes that is now induced, and given also the amount of glycogen found in the body when the animal

is killed, is it possible to assume that a quantity of glycogen equivalent to the sum of these amounts of carbohydrate can have been present in the starving animal as residual glycogen? The figures show that this assumption is impossible.

With regard to the place where the sugar that appears in phloridzin diabetes comes from, there is as yet no information; experiments, however, which I have made seem to show that the liver of an animal killed in active phloridzin diabetes, when thrown into boiling water immediately after death, may contain large quantities of preformed sugar, thus indicating that we have in the liver, at any rate, one of the sources of the sugar that appears in the urine in phloridzin diabetes.

Another point which constitutes a link between phloretin diabetes and human diabetes is the appearance in the urine in the phloretin diabetes induced during inanition of the same morbid products of proteid metabolism as are found in human diabetes. Von Mering has seen oxybutyric acid and acetone produced under these circumstances. Though I have looked for these, I have failed to find them, but I have seen in two cases the red-brown coloration in urine which is obtained by ferric chloride where acet-acetic acid is present.

There is one more subject which I desire just to glance at before concluding this sketch of the researches I have been able to undertake in connection with diabetes. This is the subject of the influence of an increased or diminished degree of venosity of the portal blood upon the glycogenic function of the liver. That the degree of venosity of the portal blood should have a great influence on the hepatic functions is *a priori* very probable, and this is borne out by Ebstein's experiments, in which he showed that the *post-mortem* conversion of glycogen into sugar was much retarded in an atmosphere of CO_2.

I think I have succeeded in finding a method by which the question can be studied. It is a method which it would take me too long to explain here in detail, and I am only desirous of mentioning it here because it is connected in a peculiar manner with the research scholarships of this Company, and with this Company's research scholar, the late Dr. Wooldridge, who when he died left behind him the beginnings of many things of which others will gather in the fruit. I refer to Dr. Wooldridge's method of coagulating the blood within the vessels of the living body. I have,

in a communication which is to appear in the next number of the *Journal of Physiology*, adduced, I think, sufficient reason to believe that this coagulation takes place everywhere in the body where the carbonic acid is in excess, and only there. If it turns out that I am correct in this, we shall have at our disposal in Dr. Wooldridge's method of coagulation one more method for investigating the obscure problems of diabetes, and of seeing a little further into that darkness of our ignorance of Nature which my co-research scholar, Dr. Wooldridge, made it his life work to strive to penetrate.